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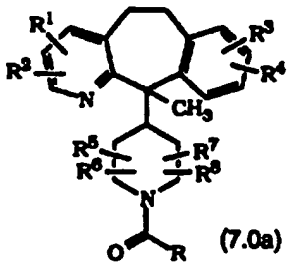
(54) Title: TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES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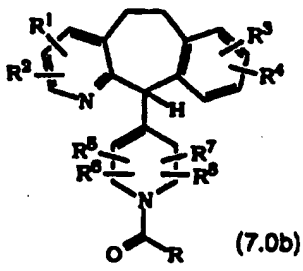
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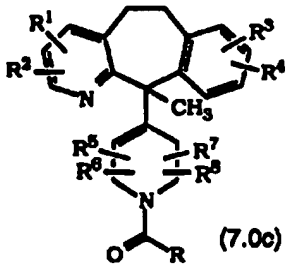
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(57) Abstract

Novel compounds of formula (7.0a), (7.0b) or (7.0c) are disclosed. Also disclosed is a method of inhibiting Ras function and therefore inhibiting the abnormal growth of cells. The method comprises administering a compound of formula (7.0a), (7.0b) or (7.0c) to a biological system. In particular, the method inhibits the abnormal growth of cells in a mammal such as a human being.

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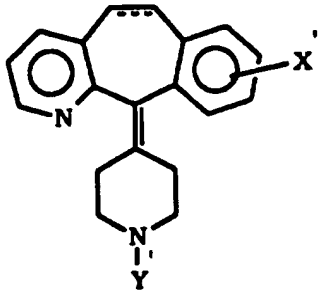
TRICYCLIC AMIDE AND UREA COMPOUNDS USEFUL FOR INHIBITION OF G-PROTEIN FUNCTION AND FOR TREATMENT OF PROLIFERATIVE DISEASES

BACKGROUND

International Publication Number WO92/11034, published July 9, 1992, discloses a method of increasing the sensitivity of a tumor to an antineoplastic agent, which tumor is resistant to the antineoplastic agent, by the concurrent administration of the antineoplastic agent and a potentiating agent of the formula:



wherein the dotted line represents an optional double bond, X' is hydrogen or halo, and Y' is hydrogen, substituted carboxylate or substituted sulfonyl. For example, Y' can be, amongst others, -COOR' wherein R' is C1 to C6 alkyl or substituted alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl or -2, -3, or -4 piperidyl or N-substituted piperidyl. Y' can also be, amongst others, SO_2R' wherein R' is C1 to C6 alkyl, phenyl, substituted phenyl, C7 to C12 aralkyl or substituted aralkyl. Examples of such potentiating agents include 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines such as Loratadine.

Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes

this modification, farnesyl protein transferase, have therefore been suggested as anticancer agents for tumors in which Ras contributes to transformation. Mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993).

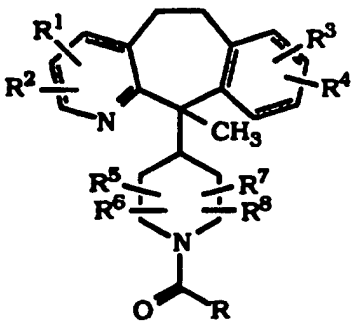
In view of the current interest in inhibitors of farnesyl protein transferase, a welcome contribution to the art would be compounds useful for the inhibition of farnesyl protein transferase. Such a contribution is provided by this invention.

SUMMARY OF THE INVENTION

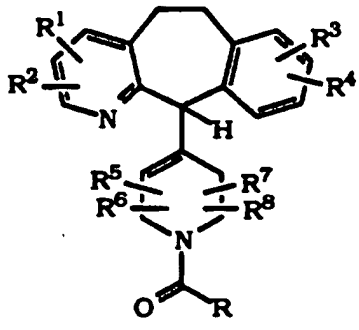
Inhibition of farnesyl protein transferase by tricyclic compounds of this invention has not been reported previously. Thus, this invention provides a method for inhibiting farnesyl protein transferase using tricyclic compounds of this invention which: (i) potently inhibit farnesyl protein transferase, but not geranylgeranyl protein transferase I, in vitro; (ii) block the phenotypic change induced by a form of transforming Ras which is a farnesyl acceptor but not by a form of transforming Ras engineered to be a geranylgeranyl acceptor; (iii) block intracellular processing of Ras which is a farnesyl acceptor but not of Ras engineered to be a geranylgeranyl acceptor; and (iv) block abnormal cell growth in culture induced by transforming Ras. Several compounds of this invention have been demonstrated to have anti-tumor activity in animal models.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of this invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) expressing an activated Ras oncogene; (2) tumor cells in which the Ras protein is activated as a result of oncogenic mutation in another gene; and (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

The compounds useful in the claimed methods are novel compounds represented by Formula (7.0a), (7.0b) or (7.0c):



(7.0a),



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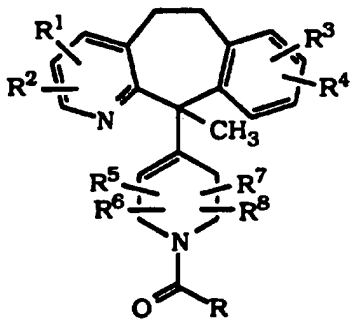
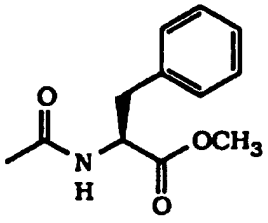
or



(7.0c)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$ (e.g., $-OCH_3$), $-COR^{10}$, $-SR^{10}$ (e.g., $-SCH_3$ and $-SCH_2C_6H_5$), $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2, e.g., $-SOCH_3$ and $-SO_2CH_3$), -SCN, $-N(R^{10})_2$, $-NR^{10}R^{11}$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$,



$-SR^{11}C(O)OR^{11}$ (e.g., $-SCH_2CO_2CH_3$), $-SR^{11}N(R^{75})_2$ wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$ (e.g., $-S(CH_2)_2NHC(O)O$-t-butyl and $-S(CH_2)_2NH_2$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio (e.g., alkyl substituted tetrazol5-ylthio such as 1-methyl-tetrazol-5-ylthio), alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken

together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring (Ring III);

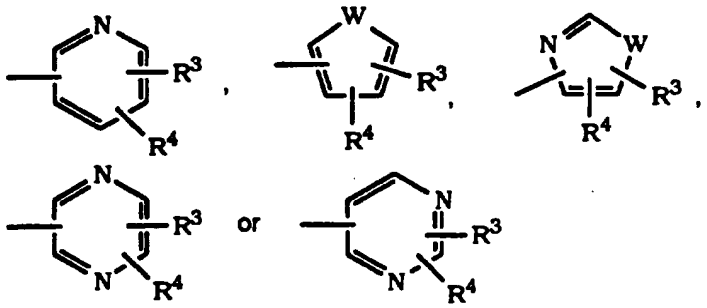
R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl (e.g., benzyl);

R^{11} represents alkyl or aryl;

R represents R^{40}, R^{42}, R^{44}, or R^{54}, as defined below;

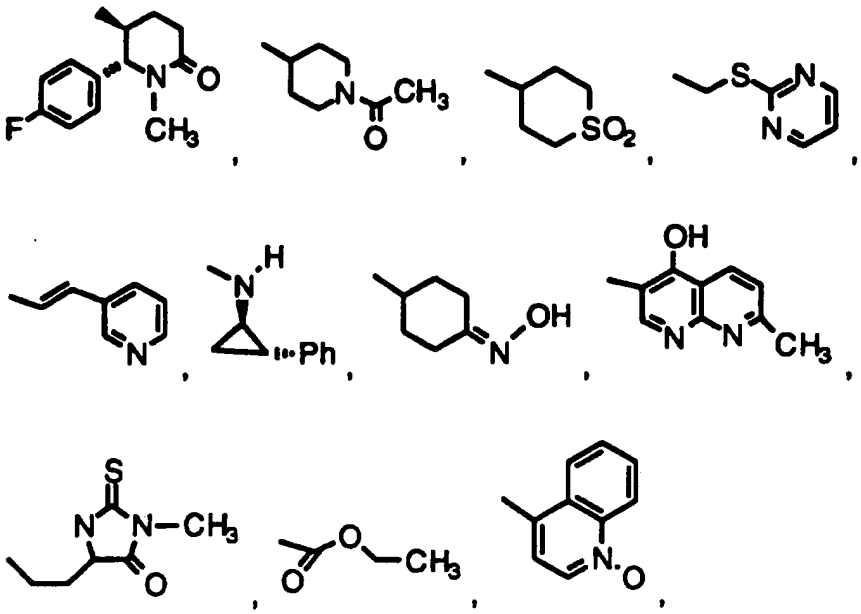
R^{40} represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents



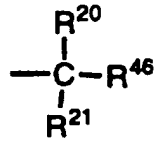
wherein R^3 and R^4 are as previously defined and W is O, S or NR^{10} wherein R^{10} is as defined above; said R^{40} cycloalkyl, alkenyl and alkynyl groups being optionally substituted with from 1-3 groups selected from halo, $-CON(R^{10})_2$, aryl, $-CO_2R^{10}$, $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$, $-N(R^{10})CO_2R^{11}$, $-COR^{12}$, $-NO_2$ or D, wherein -D, R^{10} and R^{11} are as defined above and R^{12} represents R^{10}, $-(CH_2)_mOR^{10}$ or $-(CH_2)_qCO_2R^{10}$ wherein R^{10} is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl R^{40} groups not containing -OH, -SH or $-N(R^{10})_2$ on a carbon containing a double or triple bond respectively; or

R^{40} represents phenyl substituted with a group selected from $-SO_2NH_2$, $-NHSO_2CH_3$, $-SO_2NHCH_3$, $-SO_2CH_3$, $-SOCH_3$, $-SCH_3$, or $-NHSO_2CF_3$, preferably, said group is located in the para (p-) position of the phenyl ring; or

R^{40} represents a group selected from



R^{42} represents



wherein R^{20}, R^{21} and R^{46} are each independently selected from the group consisting of:

(1) H;

(2) -(CH$_2$)$_q$SC(O)CH$_3$ wherein q is 1 to 3 (e.g., -CH$_2$SC(O)CH$_3$);

(3) -(CH$_2$)$_q$OSO$_2$CH$_3$ wherein q is 1 to 3 (e.g., -CH$_2$OSO$_2$CH$_3$);

(4) -OH;

(5) -CS(CH$_2$)$_w$(substituted phenyl) wherein w is 1 to 3 and the substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl (e.g., -C-S-CH$_2$-4-methoxyphenyl);

(6) -NH$_2$;

(7) -NHCBZ (wherein CBZ stands for carbonylbenzyloxy--i.e., CBZ represents -C(O)OCH$_2$C$_6$H$_5$);

(8) -NHC(O)OR^{22} wherein R^{22} is an alkyl group having from 1 to 5 carbon atoms (e.g., R^{22} is t-butyl thus forming -NHBOC wherein BOC

stands for tert-butyloxycarbonyl--i.e., BOC represents $-C(O)OC(CH_3)_3$), or R^{22} represents phenyl substituted with 1 to 3 alkyl groups (e.g., 4-methylphenyl);

(9) alkyl (e.g., ethyl);

(10) $-(CH_2)_k$phenyl wherein k is 1 to 6, usually 1 to 4 and preferably 1 (e.g., benzyl);

(11) phenyl;

(12) substituted phenyl (i.e., phenyl substituted with from 1 to 3 substituents, preferably one) wherein the substituents are selected from the group consisting of: halo (e.g., Br, Cl, or I, with Br being preferred); NO_2; -OH; $-OCH_3$; $-NH_2$; $-NHR^{22}$; $-N(R^{22})_2$; alkyl (e.g., alkyl having from 1 to 3 carbons with methyl being preferred); $-O(CH_2)_t$phenyl (wherein t is from 1 to 3 with 1 being preferred); and $-O(CH_2)_t$substituted phenyl (wherein t is from 1 to 3 with 1 being preferred); examples of substituted phenyls include, but are not limited to, p-bromophenyl, m-nitrophenyl, o-nitrophenyl, m-hydroxy-phenyl, o-hydroxyphenyl, methoxyphenyl, p-methylphenyl, m-methyl-phenyl, and $-OCH_2C_6H_5$;

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms (e.g., adamantyl and norbornyl);

(16) cycloalkyl having from 5 to 7 carbon atoms (e.g., cyclopentyl, and cyclohexyl);

(17) heteroaryl (e.g., pyridyl, and pyridyl N-oxide);

(18) hydroxyalkyl (e.g., $-(CH_2)_v$OH wherein v is 1 to 3, such as, for example, $-CH_2OH$);

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), $-S(O)_tR^{11}$, or any of the substituents given above for said substituted phenyl, and said substitutents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

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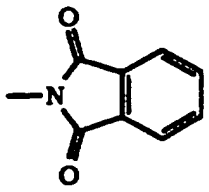
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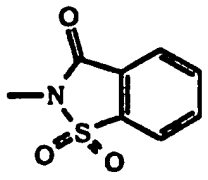
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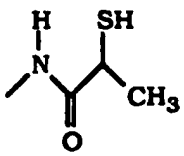
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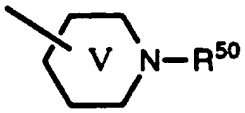
(23) -NHC(O)-$(CH_2)_k$-phenyl or -NH(O)-$(CH_2)_k$-substitued phenyl, wherein said k is as defined above (i.e., 1-6, usually 1-4 and preferably 1);

(24) piperidine Ring V: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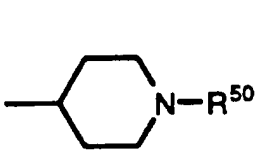
wherein R^{50} represents H, alkyl (e.g., methyl), alkylcarbonyl (e.g., $CH_3C(O)$-), alkyloxycarbonyl (e.g., -C(O)O-t-C_4H_9, -$C(O)OC_2H_5$, and -$C(O)OCH_3$), haloalkyl (e.g., trifluromethyl), or --C(O)NH(R^{10}) wherein R^{10} is H or alkyl; Ring V includes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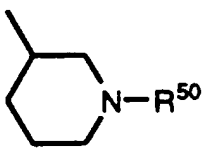
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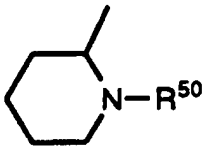
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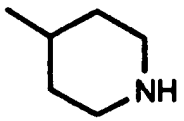
examples of Ring V include: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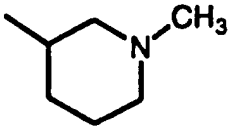
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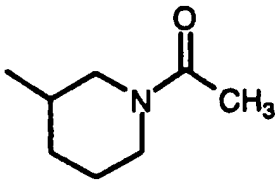
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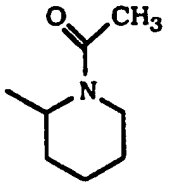
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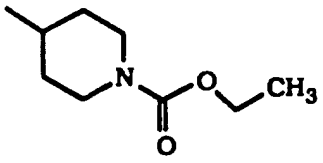
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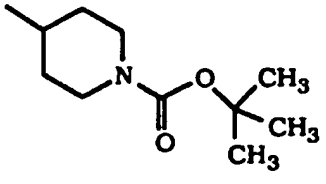
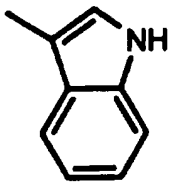
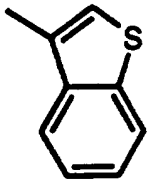
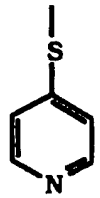

;

(25) -NHC(O)$CH_2C_6H_5$ or -NHC(O)CH_2-substituted-C_6H_5, for example -NHC(O)CH_2-p-hydroxyphenyl, -NHC(O)CH_2-m-hydroxyphenyl, and -NHC(O)CH_2-o-hydroxyphenyl;

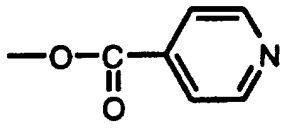
(26) -NHC(O)OC_6H_5;

(27) (28) (29)

;

(30) -OC(O)-heteroaryl, for example



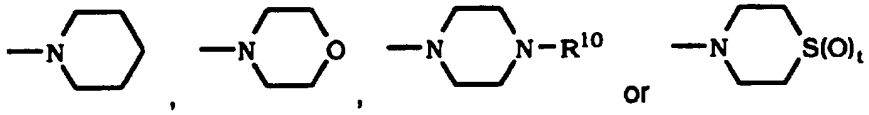
;

(31) -O-alkyl (e.g., $-OCH_3$);

(32) $-CF_3$;

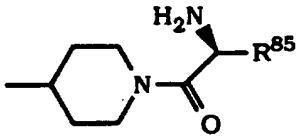
(33) -CN;

(34) a heterocycloalkyl group of the formula



; and

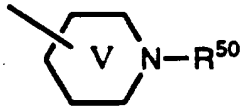
(35) a piperidinyl group of the formula



wherein R^{85} is H, alkyl, or alkyl substituted by -OH or $-SCH_3$; or

R^{20} and R^{21} taken together form a =O group and the remaining R^{46} is as defined above; or

two of R^{20}, R^{21} and R^{46} taken together form piperidine Ring V

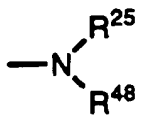


,

wherein R^{50} and Ring V are as defined above;

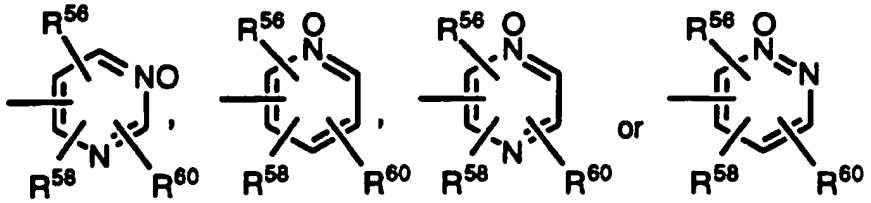
with the proviso R^{46}, R^{20}, and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom (i.e., R^{46}, R^{20}, and R^{21} are selected such that the carbon atom to which they are bound contains 0 or 1 heteroatom);

R^{44} represents



wherein R^{25} represents heteroaryl (e.g., pyridyl or pyridyl N-oxide) or aryl (e.g., phenyl and substituted phenyl); and R^{48} represents H or alkyl (e.g., methyl);

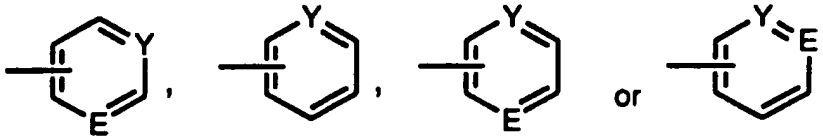
R^{54} represents an N-oxide heterocyclic group of the formula (i), (ii), (iii) or (iv):



(i) (ii) (iii) (iv)

wherein R^{56}, R^{58}, and R^{60} are the same or different and each is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-C(O)R^{10}$, $-SR^{10}$, $-S(O)_eR^{11}$ (wherein e is 1 or 2), $-N(R^{10})_2$, $-NO_2$, $-CO_2R^{10}$, $-OCO_2R^{11}$, $-OCOR^{10}$, alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with $-OR^{10}$, $-SR^{10}$ or $-N(R^{10})_2$ and which alkenyl may be substituted with OR^{11} or SR^{11}; or

R^{54} represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiia) or (iva):

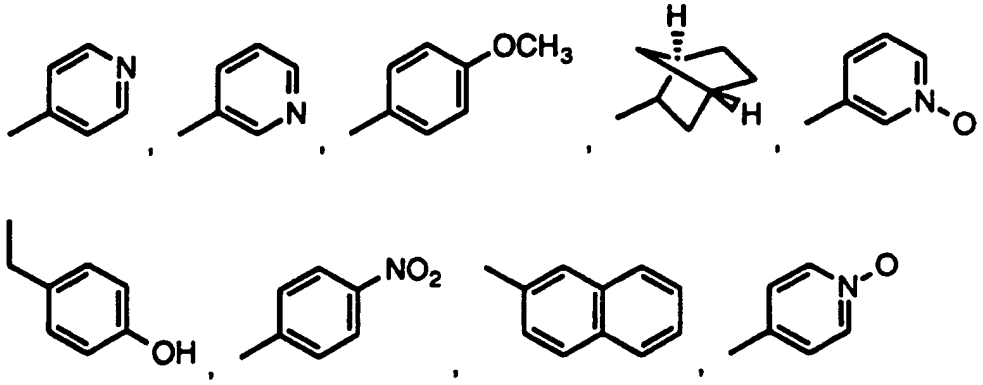


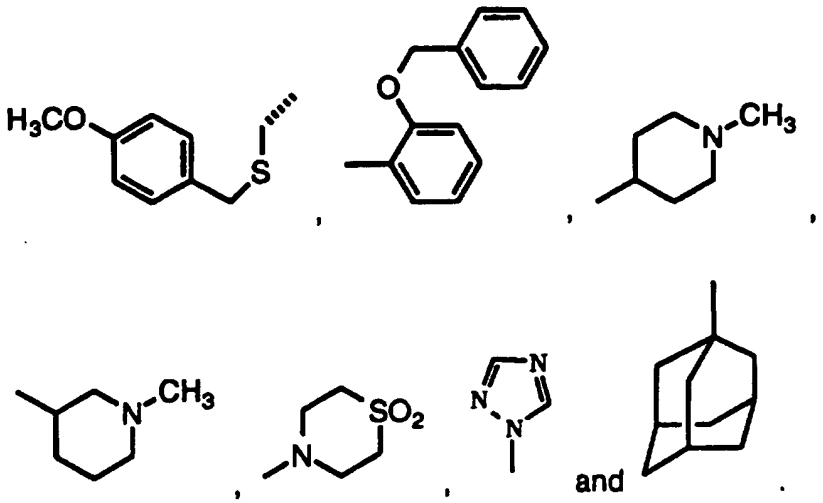
(ia) (iia) (iiia) (iva)

wherein Y represents N^+-O^- and E represents N; or

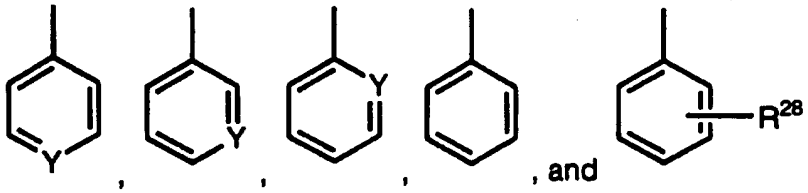
R^{54} represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia), (iiia) or (iva).

Examples of R^{20}, R^{21}, and R^{46} for the above formulas include:





Examples of R^{25} groups include:



wherein Y represents N or NO, R^{28} is selected from the group consisting of: C_1 to C_4 alkyl, halo, hydroxy, NO_2, amino ($-NH_2$), $-NHR^{30}$, and $-N(R^{30})_2$ wherein R^{30} represents C_1 to C_6 alkyl.

This invention also provides a method for inhibiting tumor growth by administering an effective amount of the tricyclic compounds, described herein, to a mammal (e.g., a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated Ras oncogene by the administration of an effective amount of the above described compounds. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g., lung adenocarcinoma), pancreatic cancers (e.g., pancreatic carcinoma such as, for example, exocrine pancreatic carcinoma), colon cancers (e.g., colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), bladder carcinoma and epidermal carcinoma.

It is believed that this invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes--i.e., the Ras gene itself is not activated by mutation to an oncogenic form--with said inhibition being accomplished by the administration of an

effective amount of the tricyclic compounds described herein, to a mammal (e.g., a human) in need of such treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which Ras is activated due to mutation or overexpression of tyrosine kinase oncogenes (e.g., neu, src, abl, lck, and fyn), may be inhibited by the tricyclic compounds described herein.

The compounds of this invention inhibit farnesyl protein transferase and the farnesylation of the oncogene protein Ras. This invention further provides a method of inhibiting ras farnesyl protein transferase, in mammals, especially humans, by the administration of an effective amount of the tricyclic compounds described above. The administration of the compounds of this invention to patients, to inhibit farnesyl protein transferase, is useful in the treatment of the cancers described above.

The tricyclic compounds useful in the methods of this invention inhibit the abnormal growth of cells. Without wishing to be bound by theory, it is believed that these compounds may function through the inhibition of G-protein function, such as ras p21, by blocking G-protein isoprenylation, thus making them useful in the treatment of proliferative diseases such as tumor growth and cancer. Without wishing to be bound by theory, it is believed that these compounds inhibit ras farnesyl protein transferase, and thus show antiproliferative activity against ras transformed cells.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms are used as defined below unless otherwise indicated:

M^+-represents the molecular ion of the molecule in the mass spectrum;

MH^+-represents the molecular ion plus hydrogen of the molecule in the mass spectrum;

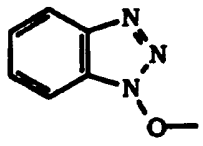
Bu-represents butyl;

Et-represents ethyl;

Me-represents methyl;

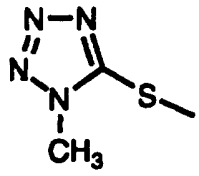
Ph-represents phenyl;

benzotriazol-1-yloxy represents



;

1-methyl-tetrazol-5-ylthio represents



;

alkyl-(including the alkyl portions of alkoxy, alkylamino and dialkylamino)-represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

alkanediyl-represents a divalent, straight or branched hydrocarbon chain having from 1 to 20 carbon atoms, preferably 1 to 6 carbon atoms, the two available bonds being from the same or different carbon atoms thereof, e.g., methylene, ethylene, ethylidene, $-CH_2CH_2CH_2-$, $-CH_2CHCH_3$, $-CHCH_2CH_3$, etc.

cycloalkyl-represents saturated carbocyclic rings branched or unbranched of from 3 to 20 carbon atoms, preferably 3 to 7 carbon atoms;

heterocycloalkyl-represents a saturated, branched or unbranched carbocylic ring containing from 3 to 15 carbon atoms, preferably from 4 to 6 carbon atoms, which carbocyclic ring is interrupted by 1 to 3 hetero groups selected from -O-, -S- or - NR^{10}-(suitable heterocycloalkyl groups including 2- or 3-tetrahydrofuranyl, 2- or 3- tetrahydrothienyl, 2-, 3- or 4-piperidinyl, 2- or 3-pyrrolidinyl, 2- or 3-piperizinyl, 2- or 4-dioxanyl, etc.);

alkenyl-represents straight and branched carbon chains having at least one carbon to carbon double bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms and most preferably from 3 to 6 carbon atoms;

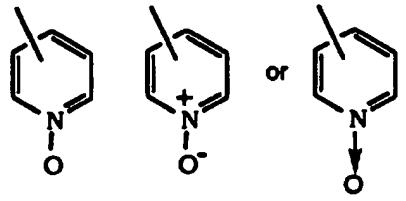
alkynyl-represents straight and branched carbon chains having at least one carbon to carbon triple bond and containing from 2 to 12 carbon atoms, preferably from 2 to 6 carbon atoms;

aryl (including the aryl portion of aryloxy and aralkyl)-represents a carbocyclic group containing from 6 to 15 carbon atoms and having at least one aromatic ring (e.g., aryl is a phenyl ring), with all available substitutable carbon atoms of the carbocyclic group being intended as possible points of attachment, said carbocyclic group being optionally

substituted (e.g., 1 to 3) with one or more of halo, alkyl, hydroxy, alkoxy, phenoxy, CF_3, amino, alkylamino, dialkylamino, $-COOR^{10}$ or $-NO_2$; and

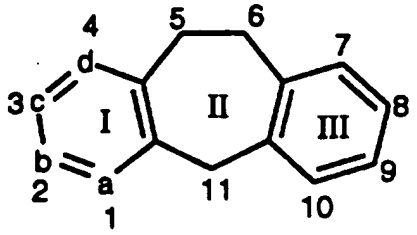
halo-represents fluoro, chloro, bromo and iodo; and

heteroaryl-represents cyclic groups, optionally substituted with R^3 and R^4, having at least one heteroatom selected from O, S or N, said heteroatom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclic groups preferably containing from 2 to 14 carbon atoms, e.g., triazolyl, 2-, 3- or 4-pyridyl or pyridyl N-oxide (optionally substituted with R^3 and R^4), wherein pyridyl N-oxide can be represented as:



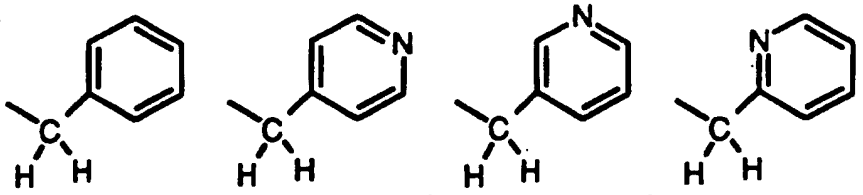
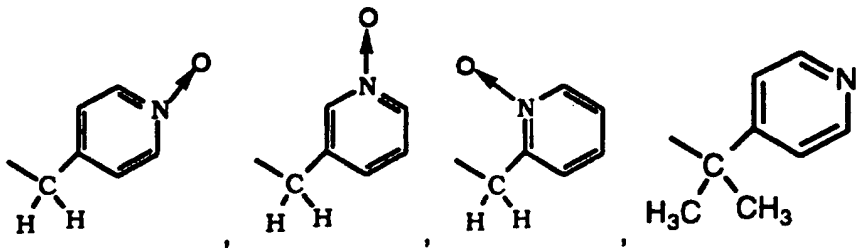
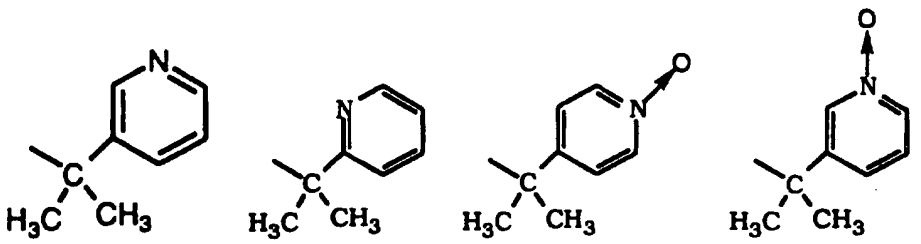
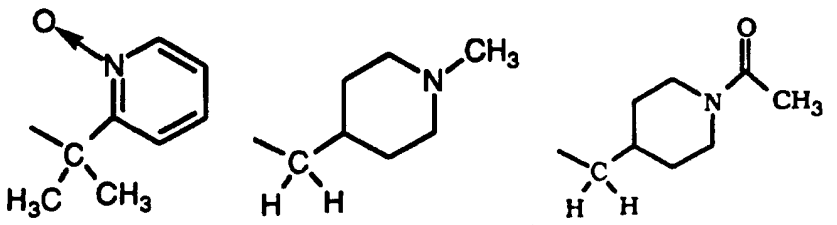
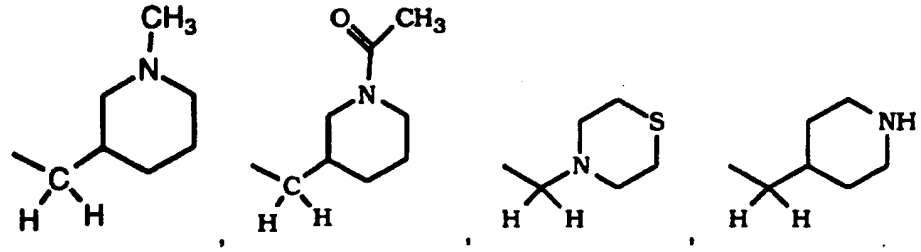
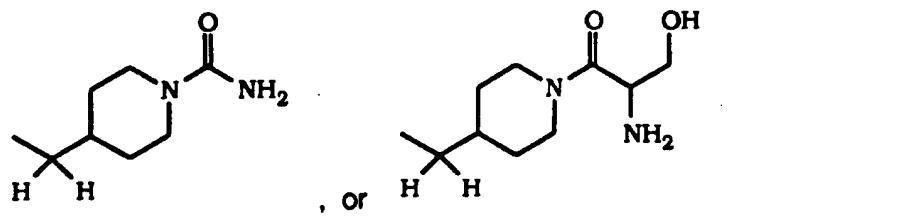
The following solvents and reagents are referred to herein by the abbreviations indicated: tetrahydrofuran (THF); ethanol (EtOH); methanol (MeOH); acetic acid (HOAc or AcOH); ethyl acetate (EtOAc); N,N-dimethylformamide (DMF); trifluoroacetic acid (TFA); trifluoroacetic anhydride (TFAA); 1-hydroxybenzotriazole (HOBT); m-chloroperbenzoic acid (MCPBA); triethylamine (Et_3N); diethyl ether (Et_2O); ethyl chloroformate ($ClCO_2Et$); 1-(3-dimethylaminopropyl)-3-ethyl carbodiimde hydrochloride (DEC).

Reference to the position of the substituents R^1, R^2, R^3, and R^4 is based on the numbered ring structure:

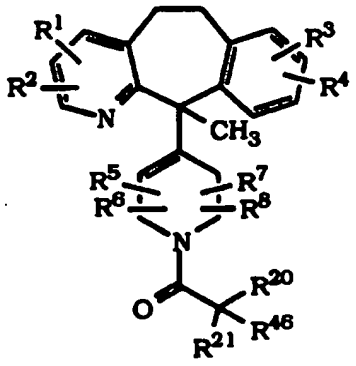


For example, R^1 can be at the C-4 position and R^2 can be at the C-2 or C-3 position. Also, for example, R^3 can be at the C-8 position and R^4 can be at the C-9 position.

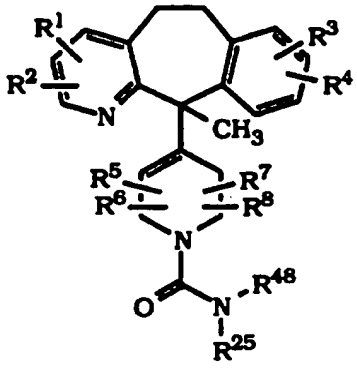
Examples of the R^{42} groups include:

Compounds of formula 7.0c include:

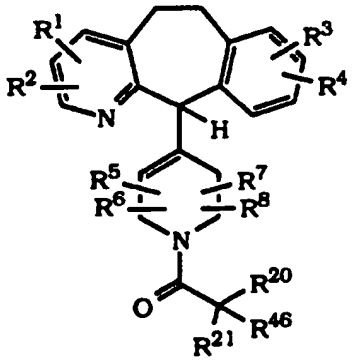


(7.0e) and

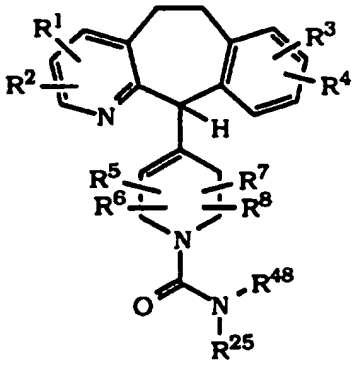


(7.0f);

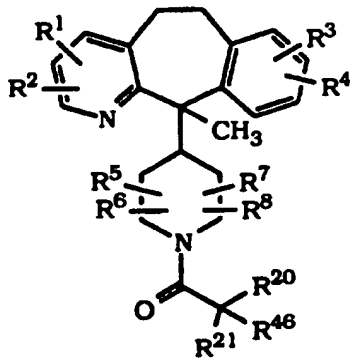
compounds of the formula 7.0b include:



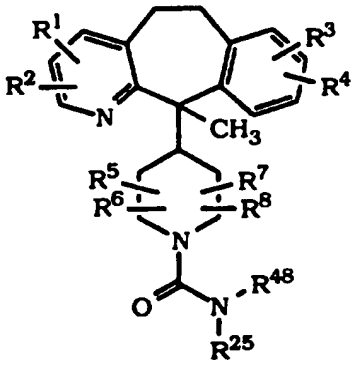
(7.0g) and



(7.0h); and compounds of the formula 7.0a include:



(7.0j) and



(7.0k).

wherein all substituents for 7.0e-7.0k are as defined for 7.0a-7.0c.

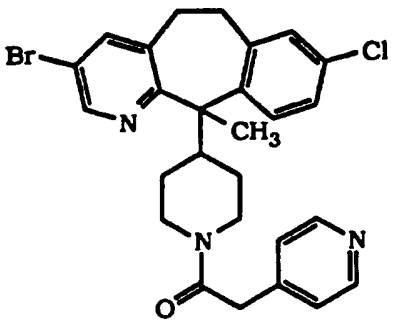
Preferably for compounds of the formula 7.0e, 7.0g and 7.0j the group R^{46} is selected from piperidine ring V, heteroaryl, phenyl, substituted phenyl, substituted pyridyl or substituted pyridyl N-oxide, and R^{20} and R^{21} are independently selected from H or alkyl. Most preferably R^{46} is pyridyl, pyridyl N-oxide or piperidine ring V. It is also preferred that R^{20} and R^{21} are both H or are both alkyl, preferably methyl.

Preferably for compounds of the formula 7.0f, 7.0h and 7.0k, the group R^{25} is phenyl, 3-pyridyl, 4-pyridyl, 3-pyridyl N-oxide, 4-pyridyl N-

oxide or piperidine ring V. More preferably R^{48} is H or methyl, with H being most preferred.

Preferably for the compounds of fomula 7.0a, 7.0b, 7.0c, 7.0e, 7.0f, 7.0g, 7.0h, 7.0j and 7.0k the groups R^5, R^6, R^7 and R^8 are H, and R^1, R^2, R^3 and R^4 are independently selected from H, halo, $-NO_2$, $-N(R^{10})_2$, alkyl, alkenyl, alkynyl, $-COR^{10}$, $-CO_2R^{10}$, $-CF_3$, $-OR^{10}$, and -CN, wherein R^{10} is as defined above for the compounds of formula 7.0a-7.0c.

Representative compounds of the present invention include:



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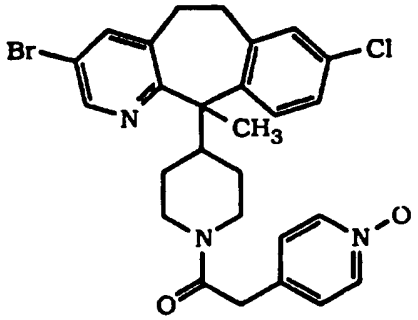

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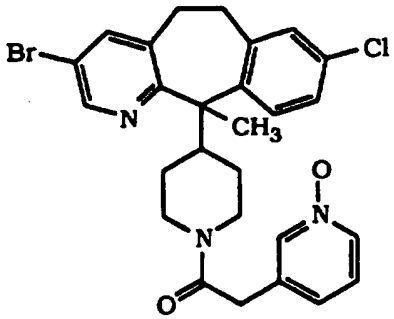

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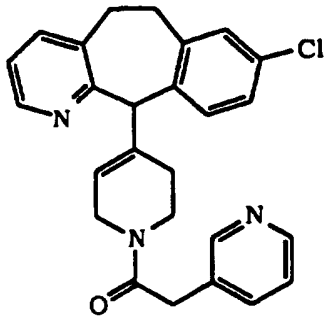

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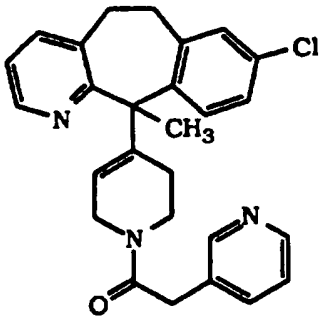

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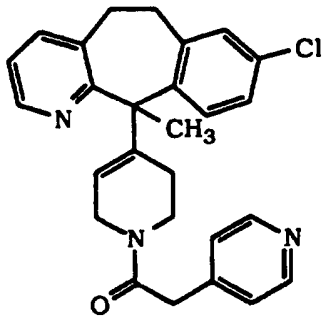

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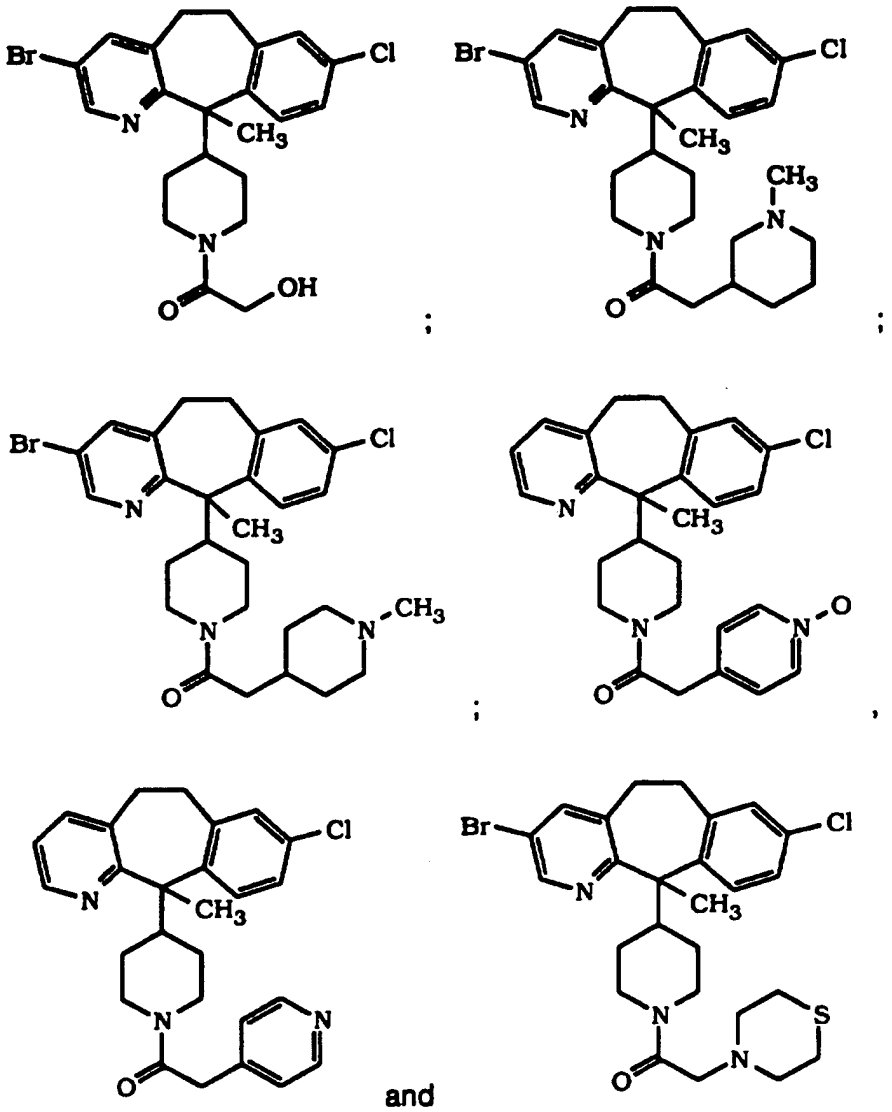


and

Preferred compounds of this invention are selected from the group consisting of the compounds of Examples: 1, 2, 2-A, 2-B, 2-C, 2-D, 2-E, 2-F, 2-K, 2-N, 2-P, and 3.

Lines drawn into the ring systems indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

Certain tricyclic compounds will be acidic in nature, e.g. those compounds which possess a carboxyl or phenolic hydroxyl group. These

compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic tricyclic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

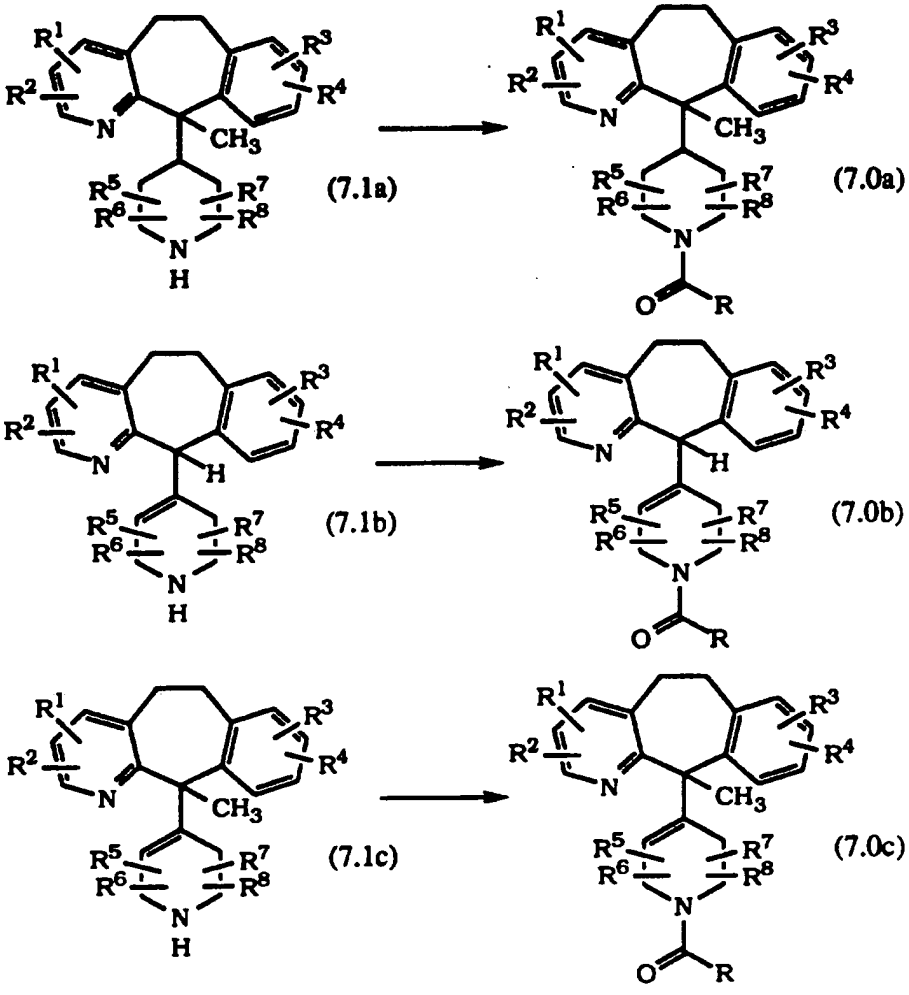
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of the invention may be made by the processes described in WO 95/10516 published April 20, 1995 (see, for example, the procedures for making compounds of formula 400.00), and by the processes described in the examples below.

On page 57 at lines 7-16 of WO 95/10516 a process is disclosed for introducing substituents at the C-3 position of pyridine Ring I of Formula 1.0 by nitrating a compound of Formula 415.00 The nitro group may then be reduced to the corresponding amine using the disclosed reagents, or powdered Zn and either $CuCl_2$ or $CuBr_2$ in aqueous EtOH.

Compounds of the formula 7.0a, 7.0b and 7.0c can be prepared from amines of the formula 7.1a, 7.1b and 7.1c, respectively, by coupling a compound of the formula 7.0a, 7.0b or 7.0c with a carboxylic acid of the

formula RCOOH via the method described in WO 95/10516 for reacting compounds of the formula 405.00.

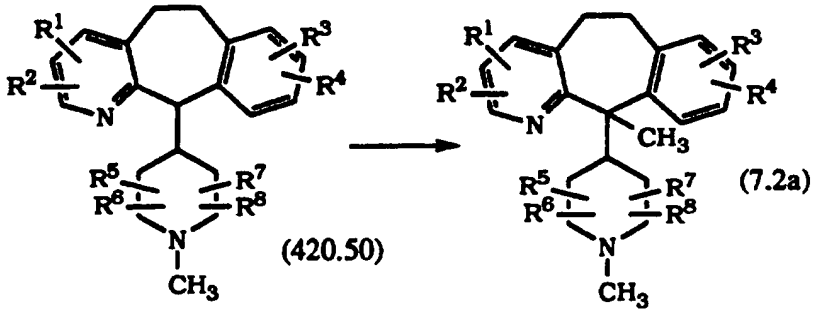


Alternatively, a compound of the formula 7.0a, 7.0b or 7.0c is treated with a compound of the formula RC(O)L, where L is a suitable leaving group, via the procedure described in WO 95/10516 for compounds of theformula 405.00.

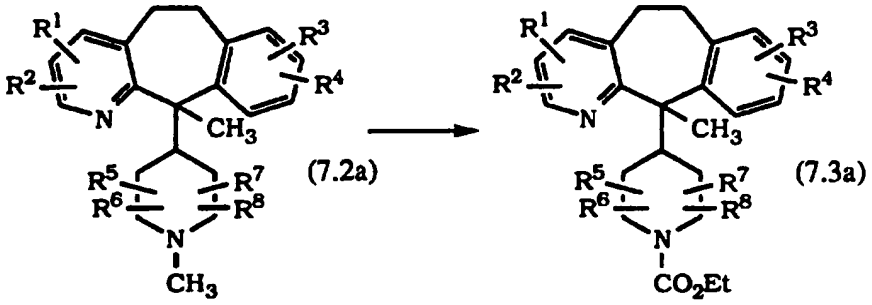
Compounds of the formula 7.1a can be prepared from a compound of the formula 420.50, (i.e., a compound of the formula 420.00, of WO 95/10516, wherein A and B are both H, no double bond is present between carbons 5 and 6, or between carbon 11 and X, X is CH, and the N-alkyl group is a methyl group) as shown in Reaction Scheme 1.

Reaction Scheme 1

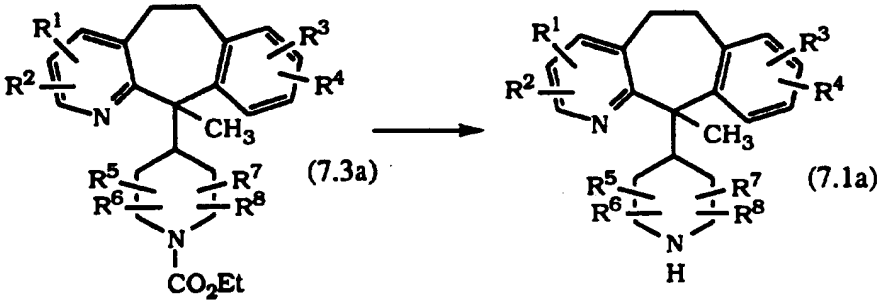
Step A:



Step B:



Step C:



In Step A of Reaction Scheme 1, a compound of the formula 420.50 is reacted with a strong base, such as an lithium diisopropylamide or an alkyllithium reagent (e.g., n-butyllithium), at -100° to -10°C, preferably at -80° to -20°C, then treated with methyl iodide to form a compound of formula 7.2a.

In Step B of Reaction Scheme 1, a compound of the formula 7.2a is converted to a compound of the formula 7.3a via substantially the same procedure as described in WO 95/10516 for formation of compounds of the formula 415.00.

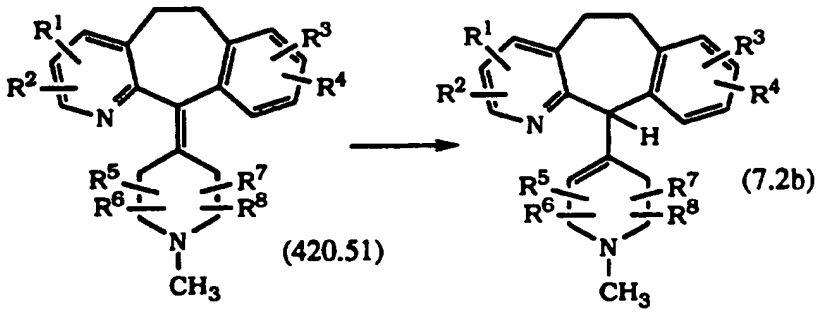
In Step C of Reaction Scheme 1, a compound of the formula 7.3a is hydrolyzed via essentially the same procedure as described in WO

95/10516 for formation of compounds of formula 405.00, to form a compound of the formula 7.1a.

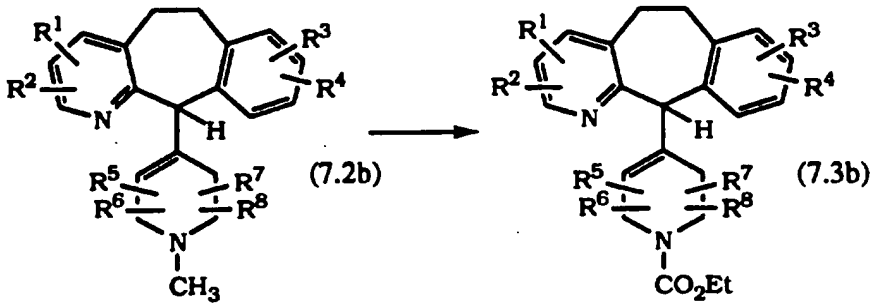
Compounds of the formula 7.1b can be prepared from a compound of the 420.51 (i.e., a compound of the formula 420.00, of WO 95/10516, wherein A and B are both H, no double bond is present between carbons 5 and 6, a double bond is present between carbon 11 and X, X is C, and the N-alkyl group is a methyl group) via the process shown in Reaction Scheme 2.

Reaction Scheme 2

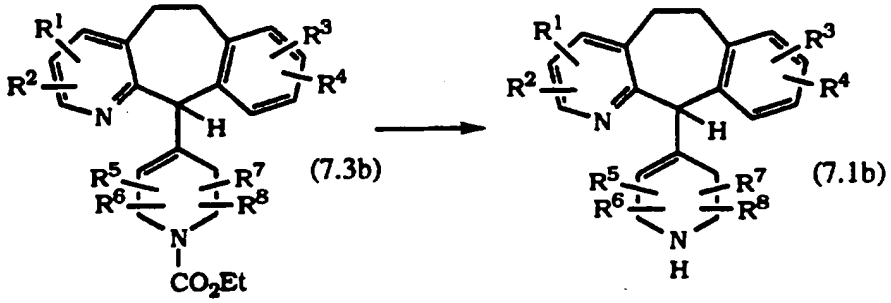
Step A:



Step B:



Step C:



In Step A of Reaction Scheme 2, a compound of the formula 420.51 is reacted with a strong base, such as an lithium diisopropylamide or an alkyllithium reagent (e.g., n-butyllithium), at -100° to -10°C, preferably at

-80° to -20°C, then treated with a protic solvent, such as an alcohol, preferably MeOH, to form a compound of formula 7.2b.

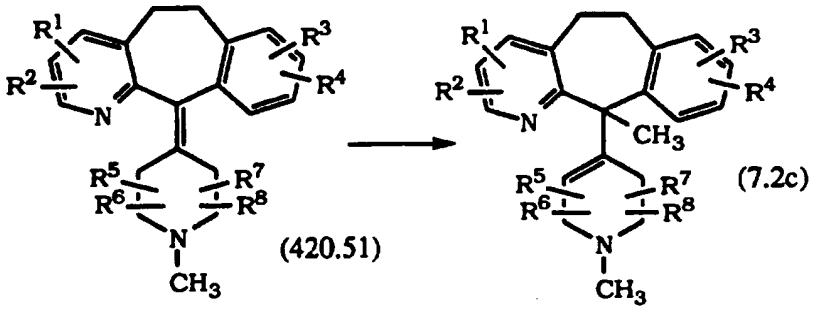
In Step B of Reaction Scheme 2, a compound of the formula 7.2b is converted to a compound of the formula 7.3b via substantially the same procedure as described in WO 95/10516 for formation of compounds of the formula 415.00.

In Step C of Reaction Scheme 2, a compound of the formula 7.3b is hydrolyzed via essentially the same procedure as described WO 95/10516, for formation of compounds of formula 405.00, to form a compound of the formula 7.1b.

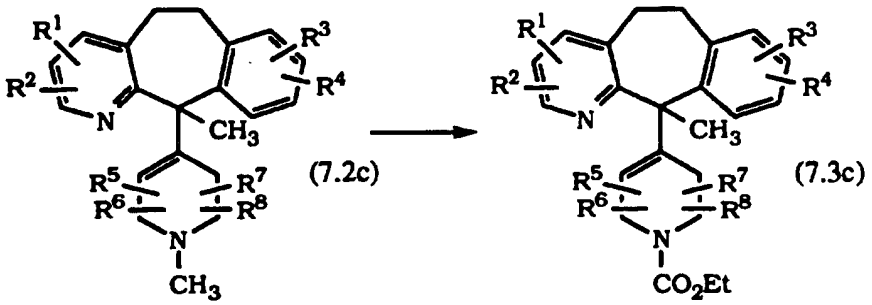
Compounds of the formula 7.1c can be prepared from a compound of the 420.51 via the process shown in Reaction Scheme 3.

Reaction Scheme 3

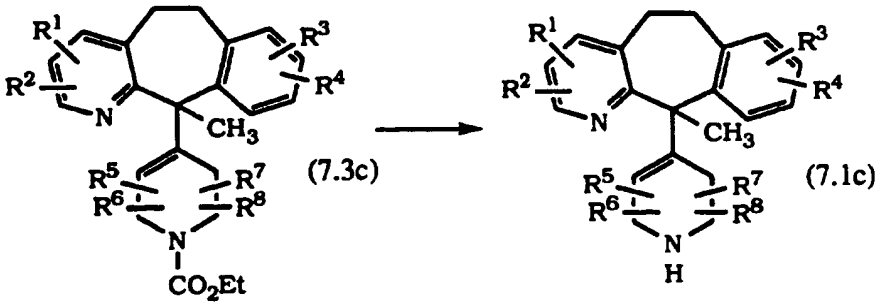
Step A:



Step B:



Step C:



In Step A of Reaction Scheme 3, a compound of the formula 420.51 is reacted with a strong base, such as an lithium diisopropylamide or an alkyllithium reagent (e.g., n-butyllithium), at -100° to -10°C, preferably at -80° to -20°C, then treated with methyl iodide to form a compound of formula 7.2c.

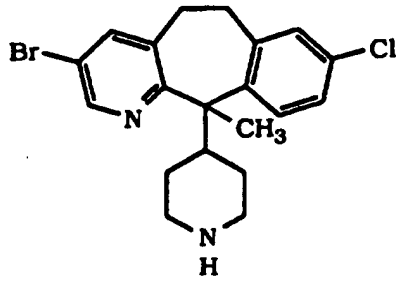
In Step B of Reaction Scheme 3, a compound of the formula 7.2c is converted to a compound of the formula 7.3c via substantially the same procedure as described in WO 95/10516 for formation of compounds of the formula 415.00.

In Step C of Reaction Scheme 1, a compound of the formula 7.3c is hydrolyzed via essentially the same procedure as described in WO 95/10516 for formation of compounds of formula 405.00, to form a compound of the formula 7.1c.

Compounds useful in this invention are exemplified by the following preparative examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

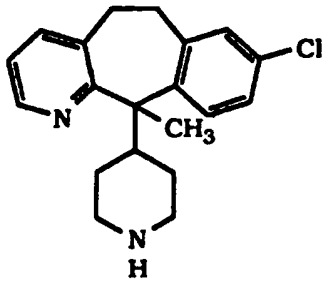
PREPARATIVE EXAMPLE 1

Using the compound of Preparative Example 3, Step C, and following essentially the same procedure as described in Example 358, Step A, of WO 95/10516, the compound:

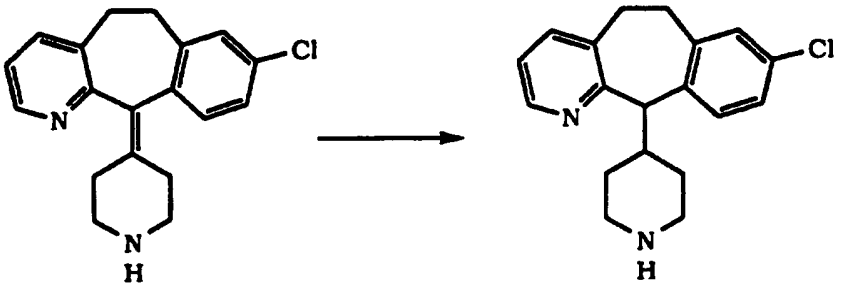


was prepared. Mass Spec.: $MH^+ = 407$

PREPARATIVE EXAMPLE 2

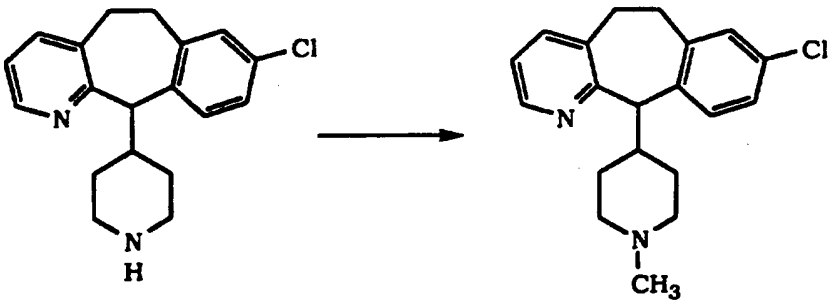


Step A:



Combine 82.0 g (0.26 mole) of the product of Preparative Example 1, Step G, of WO 95/10516, and 1 L of toluene, then add 20.06 g (0.53 mole) of $LiAlH_4$ and heat the reaction mixture at reflux overnight. Cool the mixture to room temperature and add ~1 L of Et_2O, followed by dropwise addition of saturated Na_2SO_4 (aqueous) until a precipitate forms. Filter and stir the filtrate over $MgSO_4$ for 30 minutes, then concentrate *in vacuo* to give the product compound in 83% yield. Mass Spec.: MH^+ = 313

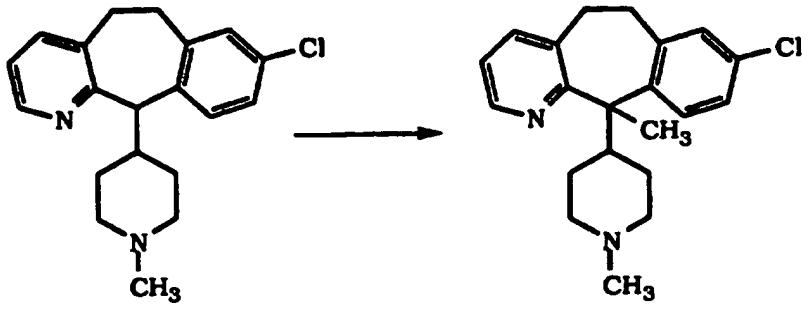
Step B:



Combine 74 g (0.24 mol) of the Product from Step A and 95 g (6.84 equiv.) of HCO_2H, then add 129 g of 7% formadehyde and heat the mixture to ~80°C for 2 hours. Cool the mixture to room temperature and basify with 25% NaOH (aqueous). Extract with EtOAc (3 X 1.3 L), dry the extracts over Na_2SO_4 and concentrate to a residue. Recystallize the

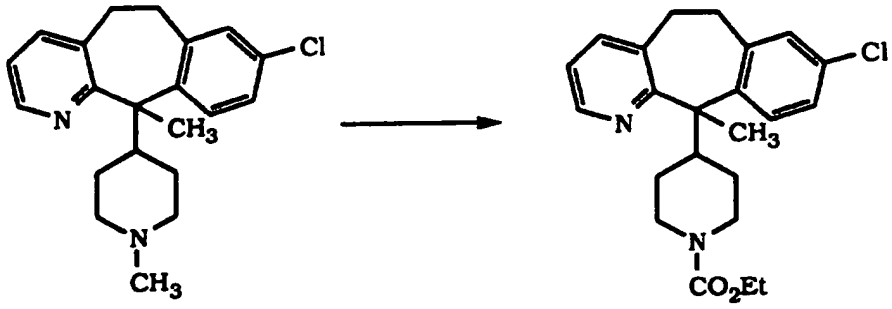
residue from iPr_2O and Et_2O to give the product compound. Mass Spec.: $MH^+ = 326$.

Step C:



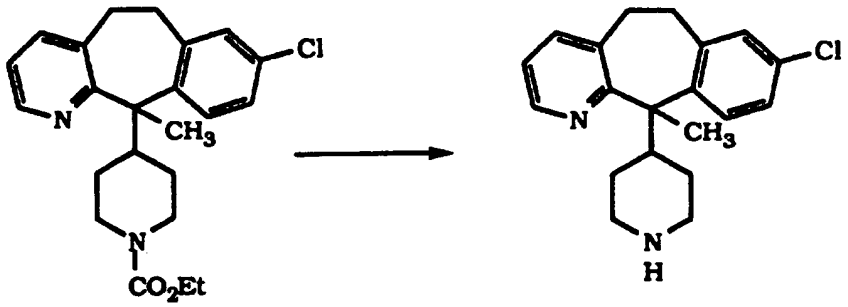
Combine 28 g of the Product of Step B and 800 mL of THF and cool to -65°C. Add a solution of 41.2 mL (1.2 equiv.) of 2.5 M n-BuLi in hexanes, stir for 1 hour at -65°C, then warm to -30 °C and stirred at that tepmerature for 1 hour. Cool to -65°C and add 10.5 mL of CH_3I, then warm to -10°C and quench with 1.5 mL of Et_2O followed by 10 mL of NH_4OH (aqueous). Dry the organic phase over K_2CO_3 and concentrate *in vacuo* to a residue. Dissolve the residue in CH_2Cl_2, wash with H_2O, dry over Na_2SO_4 and concentrate *in vacuo* to give a residue. Chromatograph (silica gel, 5% MeOH/EtOAc + NH_4OH) to give 26 g of the product compound.

Step D:



Combine 26 g of the Product of Step C, toluene, and 33 mL (3 equiv.) of Et_3N, then heat to 70°C. Slowly add 45 mL (6 equiv.) of $ClCO_2Et$ over a period of 45 min. Stir for 15 min. then pour the mixture into ice and add 100 mL of 1 N NaOH (aqueous). Extract with EtOAc, dry the extract and concentrate *in vacuo* to give 37 g of the product compound.

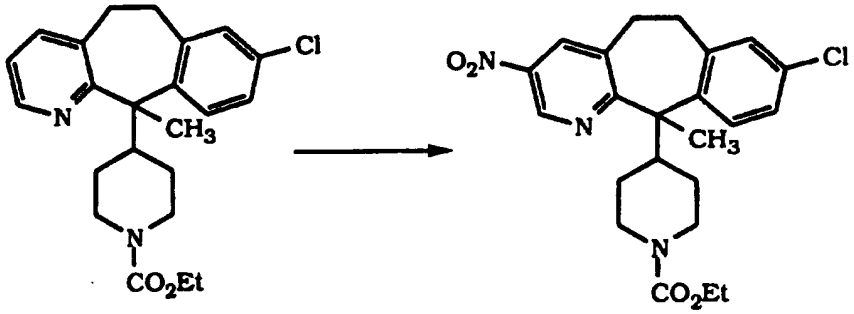
Step E:



Hydrolyze 3.5 g (8.8 mmol) of the Product of Step D, by substantially the same procedure as described for Example 358, Step A, to give 2.26 g (79% yield) of the product compound.
Mass Spec.: $MH^+ = 327$

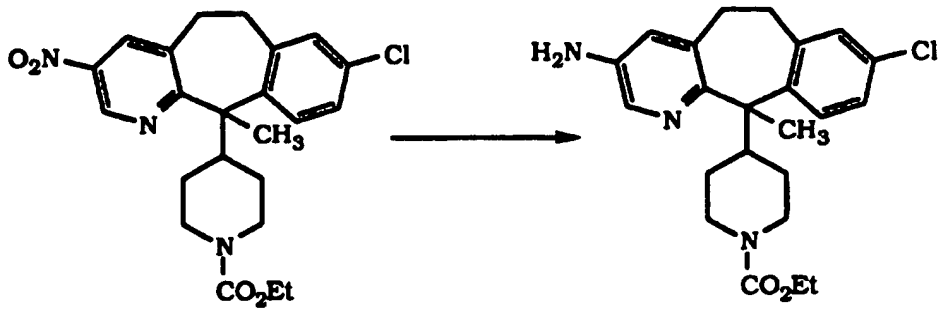
PREPARATIVE EXAMPLE 3

Step A:



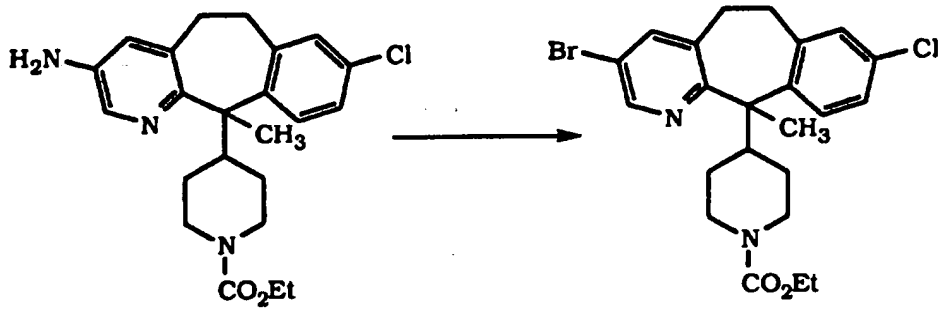
Dissolve 8.66 g (28.6 mmol) of tetra-n-butylammonium nitrate in 50 mL of CH_2Cl_2 and add 5.99 g (28.57 mmol, 2.1 mL) of TFAA. Cool to 0°C and add the mixture (via cannula) to a solution of 10.36 g (14.9 mmol) of the product of Preparative Example 2, Step D in 150 mL of CH_2Cl_2 at 0°C, then stir at 0°C for 3 hours. Allow the mixture to warm to 25°C while stirring overnight, then extract with 150 mL of saturated $NaHCO_3$ (aqueous) and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, 10% EtOc/hexane, then 20% EtOAc/hexane) to give a 57% yield of the product compound.
Mass Spec.: $MH^+ = 442$.

Step B:



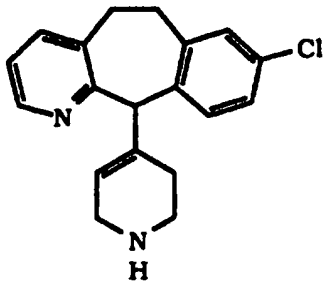
Combine 5.9 g (13.29 mmol) of the Product of Step A and 400 mL of 85% EtOH (aqueous), add 6.6 g (119 mmol) of Fe filings and 0.66 g (5.98 mmol) of $CaCl_2$, and heat at reflux for 16 hours. Filter the hot mixture through a bed of celite®, wash the celite® with 700 mL of hot EtOH. Concentrate the filtrate *in vacuo* to give a 100% yield of the product compound. Mass Spec.: $MH^+ = 414$.

Step C:

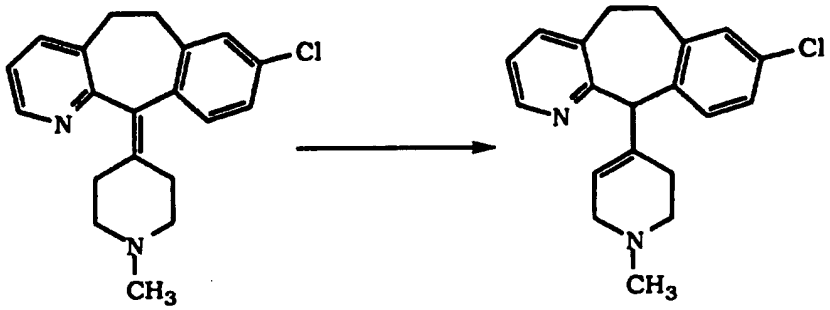


Combine 6.5 g (15.7 mmol) of the Product of Step B and 63 mL of 48% HBr, cool the mixture to -5°C and slowly (dropwise) add 4.4 mL of Br_2 bromine(4.4 mL). Stir the mixture at -5°C for 15 minutes and slowly add a solution of 3.25 g (47.1 mmol) of $NaNO_2$ in 30 mL of water. Stir for 45 minutes, then quench with 50% NaOH (aqueous) to pH ~10. Extract with EtOAc (3 x 200 mL), dry the combined extracts over Na_2SO_4 and concentrate *in vacuo* to give 6.32 g (81% yield) of the product compound. Mass Spec.: $MH^+ = 479$

PREPARATIVE EXAMPLE 4

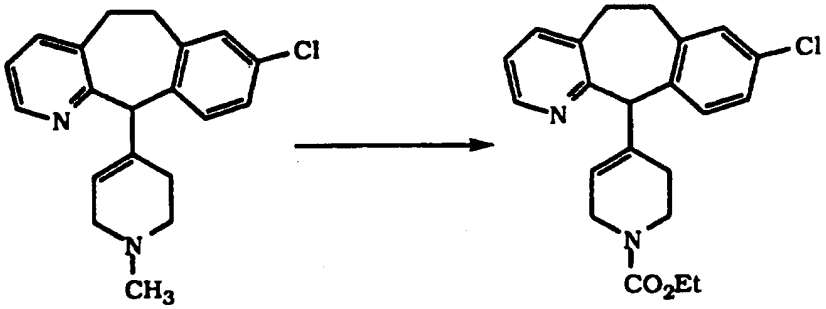


Step A:



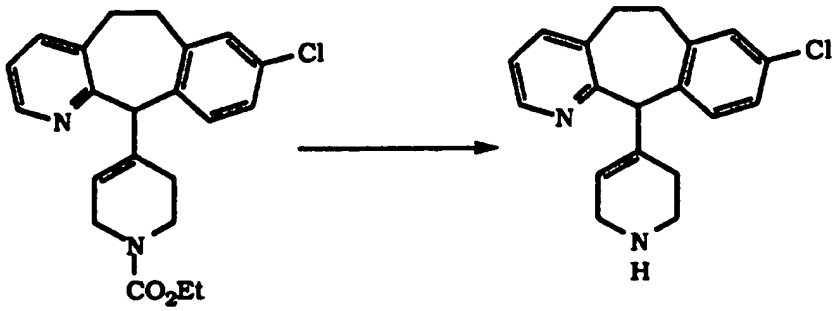
Dissolve 9.8 g (30.2 mmol) of the Product of Preparative Example 1, Step E, of WO 95/10516, in THF under nitrogen, cool the mixture to -15°C, then add 17.76 mL (30.3 mmol) of 2.5 M n-butyllithium in hexanes and stir for 1.5 hours. Cool the reaction mixture to -70°C and add 2.45 mL (60 mmol) of MeOH and warm to room temperature overnight. Add 300 mL of (Et_2O) and extract with water (3 x 100 mL). Dry the extracts, concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, 5% Et_3N/EtOAc) to give 6.59 g (68% yield) of the product compound.

Step B:



Treat 3 g (9.23 mmol) of the Product of Step A with 10 mL of $ClCO_2Et$ and 10 mL of Et_3N via substantially the same procedure as described in Preparative Example 2, Step D, to give 2.2 g (64% yield) of the product compound. Mass Spec.: MH^+ = 383

Step C:

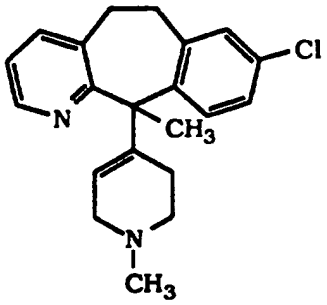


Treat the Product of Step B via substantially the same procedure as described in Preparative Example 1, Step F, of WO 95/10516, to give the product compound. Mass Spec.: $MH^+ = 310$

PREPARATIVE EXAMPLE 4A

Step A:

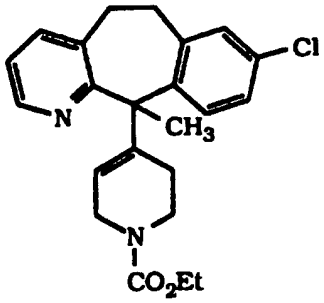
Using the Product of Preparative Example 1, Step E, of WO 95/10516, and following substantially the same procedure as described in Preparative Example 4, Step A, except that methyl iodide is used in place of MeOH, the compound:



was prepared. Mass Spec.: $MH^+ = 339$

Step B:

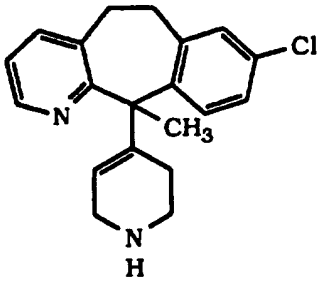
Using the compound of Preparative Example 4A, Step A, and following substantially the same procedure as described in Preparative Example 4, Step B, the compound:



was prepared. Mass Spec.: MH^+ = 397

Step C:

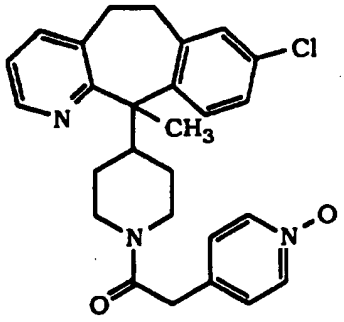
Using the compound of Preparative Example 4A, Step B, and following substantially the same procedure as described in Preparative Example 4, Step C, the compound:



was prepared. Mass Spec.: MH^+ = 325

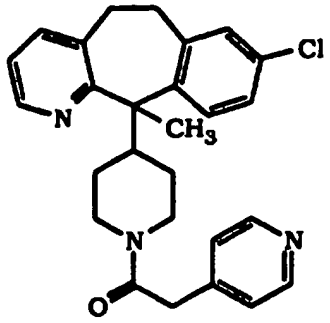
EXAMPLE 1

Using 4-pyridyl acetic acid N-oxide and the compound of Preparative Example 2, the compound:



was prepared via substantially the same procedure as described in Example 227 of WO 95/10516Mass Spec: MH^+ = 462.

EXAMPLE 2



The product of Preparative Example 2 was reacted with 4-pyridylacetic acid via substantially the same procedure as described for Example 180, of WO 95/10516, to give the product compound. Mass Spec.: $MH^+ = 446$

Using the appropriate carboxylic acid and the starting compound indicated, the compounds in Table 1 were prepared via substantially the same procedure as described for Example 2:

TABLE 1

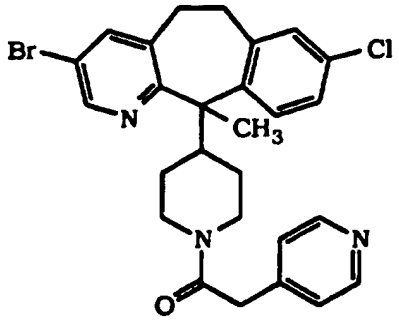
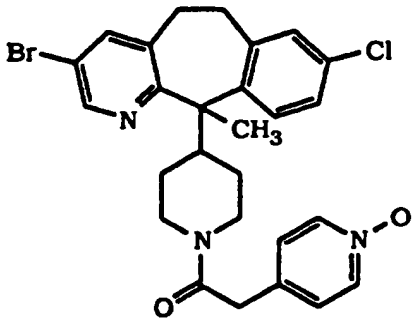
Starting Compound	Product Compound	Analytical Data
Preparative Example 1	 Example 2-A	Mass Spec.: $MH^+ = 526$
Preparative Example 1	 Example 2-B	Mass Spec.: $MH^+ = 542$

TABLE 1 - CONTINUED

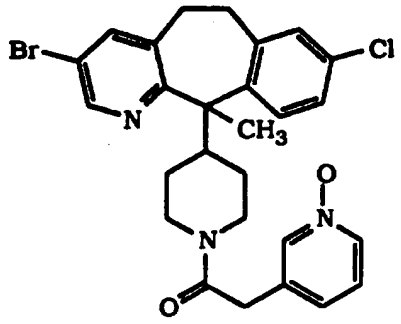
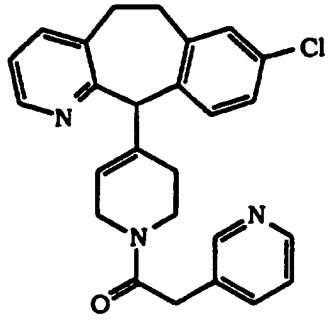
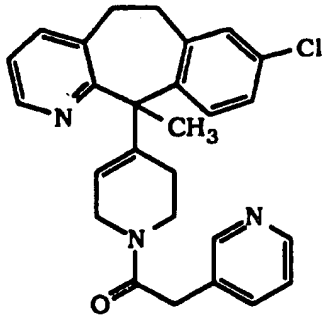
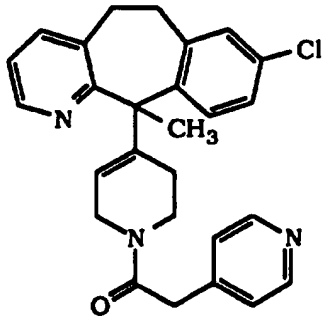
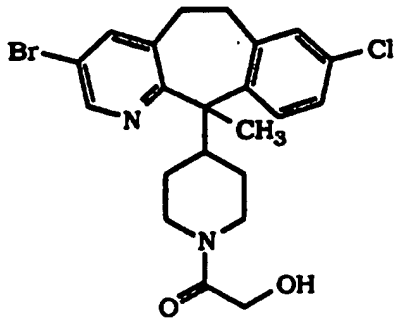
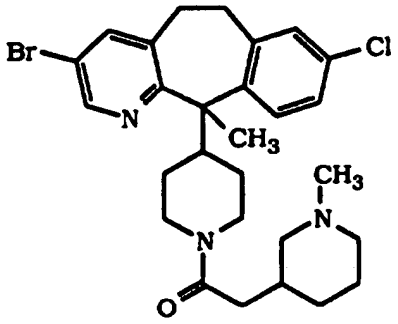
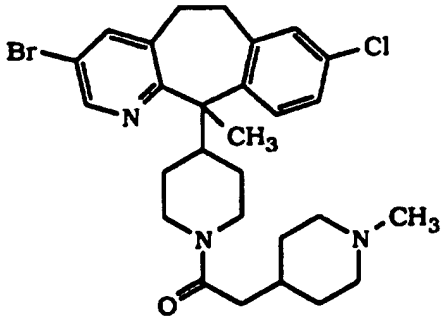
Starting Compound	Product Compound	Analytical Data
Preparative Example 1	 Example 2-C	Mass Spec.: MH+ = 542
Preparative Example 4	 Example 2-D	m.p. = 67°-69°C Mass Spec.: MH+ = 430
Preparative Example 4A	 Example 2-E	m.p. = 77°-78°C Mass Spec.: MH+ = 444
Preparative Example 4A	 Example 2-F	m.p. = 78°-79°C Mass Spec.: MH+ = 444

TABLE 1 - CONTINUED

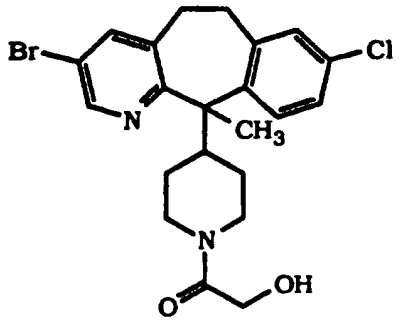
Starting Compound	Product Compound	Analytical Data
Preparative Example 1	 Example 2-K	m.p. = 108.8°-109.7°C Mass Spec.: MH^+ = 465.4
Preparative Example 1	 Example 2-N	m.p. = 164.8°-165.2°C Mass Spec.: MH^+ = 546
Preparative Example 1	 Example 2-P	m.p. = 124.2°-125°C Mass Spec.: MH^+ = 546

EXAMPLE 3

Step A:

The compound of Preparative Example 1 (0.96g) was dissolved in 20 mL of DMF by stirring at room temperature. The reaction mixture was then cooled to about 0°C, and then 4-methylmorpholine (5.0 eq), DEC (2.0 eq), HOBT (2.0 eq) and $HOCH_2COOH$ (1.5 eq) were added to the reaction mixture. The reaction mixture was kept at room temperature overnight. The DMF was removed from the mixture and the resulting mixture was

dried *in vacuo*. The crude mixture was then extracted with CH_2Cl_2 - H_2O, saturated $NaHCO_3$, 10% $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting material was purified using flash column chromatography (~ 125 mL of normal phase silica gel, 2%MeOH/NH_3-CH_2Cl_2) to give



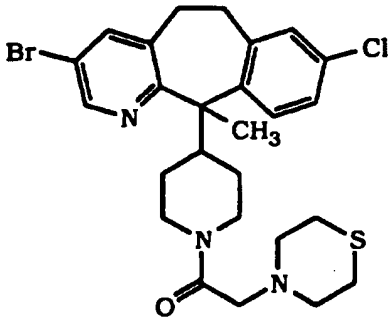
(m.p. = 108.8 - 109.7°C). Mass Spec.: MH^+ = 465

Step B:

The Product of Step A (~ 1.0g, 2.2mmol) was dissolved in 7.0 mL of $SOCl_2$ and stirred at room temperature overnight. The excess $SOCl_2$ was removed, and ~ 50 mL of CH_2Cl_2 was added and the resulting solution was concentrated to dryness (3X). Mass Spec.: MH^+ = 483

Step C:

The chloride Product of Step B (~ 0.40g) was dissolved in 28.4 mL of CH_2Cl_2 under nitrogen. Thiomorpholine (0.5 mL) was added at room temperature. When tlc indicated the reaction was complete, ~ 250 mL of CH_2Cl_2 was added to the reaction mixture, and the resulting mixture was extracted with water (~ 200 mL) and brine. The organic layer was dried over $MgSO_4$ and then the solvent was removed *in vacuo*. The resulting material was purified by flash column chromatography (~ 100 mL normal phase silica gel, 2%MeOH/NH_3-CH_2Cl_2) to give



Mass Spec.: MH^+ = 550, m.p. = 102.5°-102.9°C

ASSAYS

FPT IC_{50} (inhibition of farnesyl protein transferase in vitro enzyme assay), GGPT IC_{50} (inhibition of geranylgeranyl protein transferase in vitro enzyme assay), COS Cell IC_{50} (Cell-Based Assay) and Cell Mat Assay are determined by the assay procedures described in WO 95/10516.

TABLE 2

FPT INHIBITION

EXAMPLE	FPT IC_{50} (μM)	EXAMPLE	FPT IC_{50} (μM)
1	0.01-10	2-C	0.01-10
2	0.01-10	2-D	0.01-10
2-A	0.01-10	2-E	31%@4.5μM
2-B	0.01-10	2-F	0.01-10

TABLE 3

COMPARISON OF FPT INHIBITION AND GGPT INHIBITION

EXAMPLE	ENZYME INHIBITION FPT IC_{50} μM	ENZYME INHIBITION GGPT IC_{50} μM
2-A	0.01-10	47%@ 35μM
2-B	0.01-10	21%@ 35μM

TABLE 4

ACTIVITY IN COS CELL

Example	Inhibition of Ras Processing IC_{50} (μM)	Example	Inhibition of Ras Processing IC_{50} (μM)
2-A	0.01-10	2-N	0.01-10
2-B	0.01-10	2-P	0.01-10
2-D	10-100	3	0.01-10

TABLE 5

INHIBITION OF TUMOR CELL GROWTH - MAT ASSAY

Example	Tumor IC_{50} (μM)	Normal IC_{50} (μM)	Example	Tumor IC_{50} (μM)	Normal IC_{50} (μM)
2-A	1.6	18	2-N	8	8
2-B	10	>25	2-P	6.25	6.25
2-D	10	>50	3	>25	>25

RESULTS:

1. Enzymology:

The data demonstrate that the compounds of the invention are inhibitors of Ras-CVLS farnesylation by partially purified rat brain farnesyl protein transferase (FPT). The data also show that there are compounds of the invention which can be considered as potent (IC_{50} <10 μM) inhibitors of Ras-CVLS farnesylation by partially purified rat brain FPT.

The data also demonstrate that compounds of the invention are poorer inhibitors of geranylgeranyl protein transferase (GGPT) assayed using Ras-CVLL as isoprenoid acceptor. This selectivity is important for the therapeutic potential of the compounds used in the methods of this invention, and increases the potential that the compounds will have selective growth inhibitory properties against Ras-transformed cells.

2. Cell-Based: COS Cell Assay

Western blot analysis of the Ras protein expressed in Ras-transfected COS cells following treatment with compounds of the invention indicated that the compounds inhibit Ras-CVLS processing, causing accumulation of unprocessed Ras. Microscopic and photographic examination of the Ras-transfected COS cells following treatment with the compounds indicated that the compounds also blocked phenotypic changes induced by expression of oncogenic Ras. Cells expressing oncogenicRas-CVLS or Ras-CVLL overgrew the monolayer and formed dense foci of cells.

These results provide evidence for specific inhibition of farnesyl protein transferase, but not geranylgeranyl transferase I, by compounds of this invention in intact cells and indicate their potential to block cellular transformation by activated Ras oncogenes.

3. Cell-Based: Cell Mat Assay

Compounds of the invention also inhibited the growth of Ras-transformed tumor cells in the Mat assay without displaying cytotoxic activity against the normal monolayer.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg. to 300 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 10 mg to 2000 mg/day preferably 10 to 1000 mg/day, in two to four divided doses to block tumor growth. The compounds are non-toxic when administered within this dosage range.

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

Pharmaceutical Dosage Form Examples

EXAMPLE A

Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	7	7
	Total	253	700

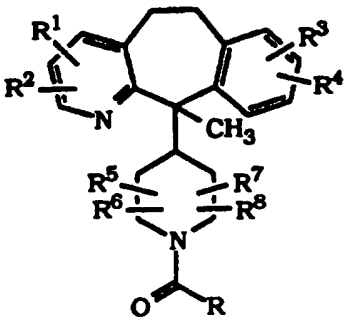
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

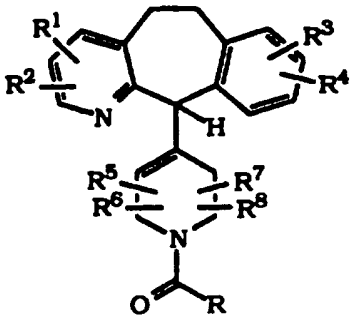
While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula (7.0a), (7.0b) or (7.0c):

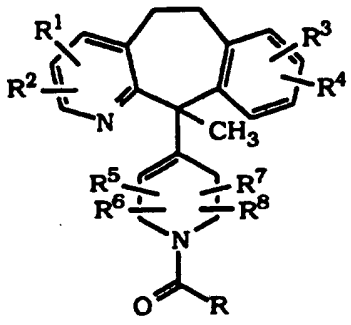


(7.0a),



(7.0b)

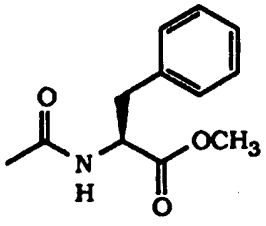
or



(7.0c)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^1 and each R^2 is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-COR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$ (wherein t is 0, 1 or 2), -SCN, $-N(R^{10})_2$, $-NO_2$, $-OC(O)R^{10}$, $-CO_2R^{10}$, $-OCO_2R^{11}$, -CN, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-CONHR^{10}$, $-CONHCH_2CH_2OH$, $-NR^{10}COOR^{11}$, $-SR^{11}C(O)OR^{11}$,



$-SR^{11}N(R^{75})_2$ (wherein each R^{75} is independently selected from H and $-C(O)OR^{11}$), benzotriazol-1-yloxy, tetrazol-5-ylthio, or substituted tetrazol-5-ylthio, alkynyl, alkenyl or alkyl, said alkyl or alkenyl group optionally being substituted with halo, $-OR^{10}$ or $-CO_2R^{10}$;

R^3 and R^4 are the same or different and each independently represents H, any of the substituents of R^1 and R^2, or R^3 and R^4 taken together represent a saturated or unsaturated C_5-C_7 fused ring to the benzene ring;

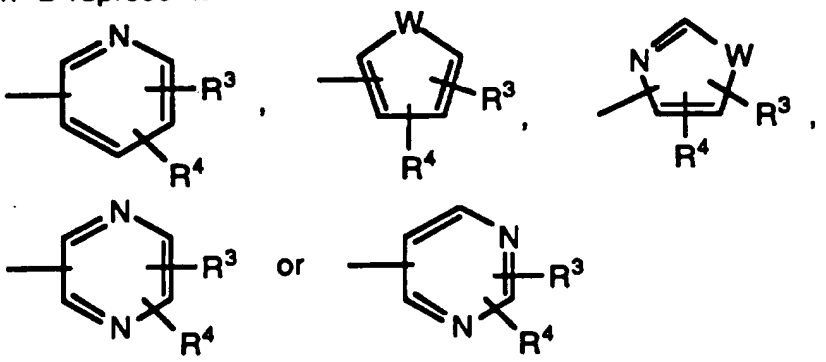
R^5, R^6, R^7 and R^8 each independently represents H, $-CF_3$, $-COR^{10}$, alkyl or aryl, said alkyl or aryl optionally being substituted with $-OR^{10}$, $-SR^{10}$, $-S(O)_tR^{11}$, $-NR^{10}COOR^{11}$, $-N(R^{10})_2$, $-NO_2$, $-COR^{10}$, $-OCOR^{10}$, $-OCO_2R^{11}$, $-CO_2R^{10}$, OPO_3R^{10} or one of R^5, R^6, R^7 and R^8 can be taken in combination with R^{40} as defined below to represent $-(CH_2)_r-$ wherein r is 1 to 4 which can be substituted with lower alkyl, lower alkoxy, $-CF_3$ or aryl, or R^5 is combined with R^6 to represent =O or =S and/or R^7 is combined with R^8 to represent =O or =S;

R^{10} represents H, alkyl, aryl, or aralkyl;

R^{11} represents alkyl or aryl;

R represents R^{40}, R^{42}, R^{44}, or R^{54}, as defined below;

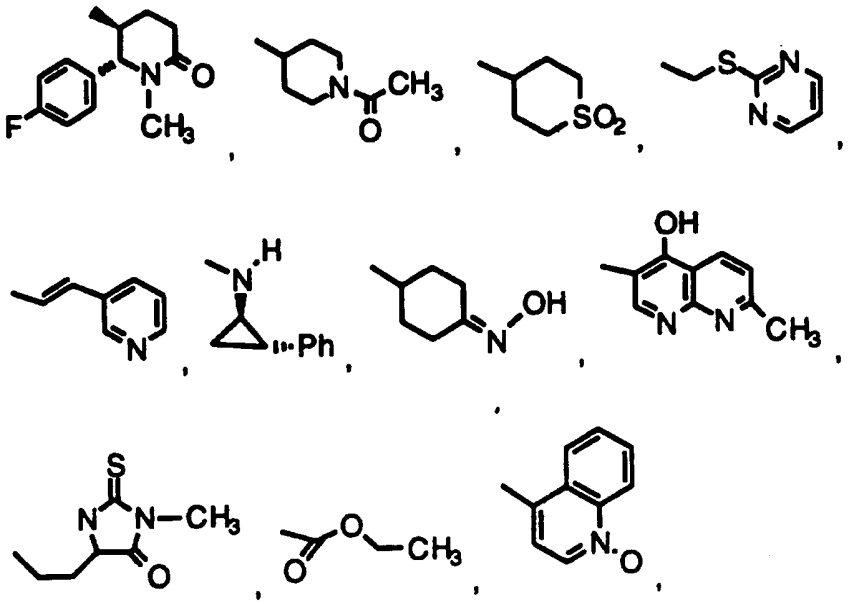
R^{40} represents H, aryl, alkyl, cycloalkyl, alkenyl, alkynyl or -D wherein -D represents



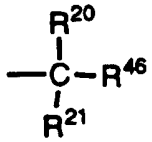
wherein R^3 and R^4 are as previously defined and W is O, S or NR^{10} wherein R^{10} is as defined above; said R^{40} cycloalkyl, alkenyl and alkynyl groups being optionally substituted with from 1-3 groups selected from halo, $-CON(R^{10})_2$, aryl, $-CO_2R^{10}$, $-OR^{12}$, $-SR^{12}$, $-N(R^{10})_2$, $-N(R^{10})CO_2R^{11}$, $-COR^{12}$, $-NO_2$ or D, wherein -D, R^{10} and R^{11} are as defined above and R^{12} represents R^{10}, $-(CH_2)_mOR^{10}$ or $-(CH_2)_qCO_2R^{10}$ wherein R^{10} is as previously defined, m is 1 to 4 and q is 0 to 4; said alkenyl and alkynyl R^{40} groups not containing -OH, -SH or $-N(R^{10})_2$ on a carbon containing a double or triple bond respectively; or

R^{40} represents phenyl substituted with a group selected from $-SO_2NH_2$, $-NHSO_2CH_3$, $-SO_2NHCH_3$, $-SO_2CH_3$, $-SOCH_3$, $-SCH_3$, or $-NHSO_2CF_3$, preferably, said group is located in the para position of the phenyl ring; or

R^{40} represents a group selected from



R^{42} represents



wherein R^{20}, R^{21} and R^{46} are each independently selected from the group consisting of:

(1) H;

(2) -(CH$_2$)$_q$SC(O)CH$_3$ wherein q is 1 to 3;

(3) -(CH$_2$)$_q$OSO$_2$CH$_3$ wherein q is 1 to 3;

(4) -OH;

(5) -CS(CH$_2$)$_w$(substituted phenyl) wherein w is 1 to 3 and the substitutents on said substituted phenyl group are the same substitutents as described below for said substituted phenyl;

(6) -NH$_2$;

(7) -NHCBZ;

(8) -NHC(O)OR^{22} wherein R^{22} is an alkyl group having from 1 to 5 carbon atoms, or R^{22} represents phenyl substituted with 1 to 3 alkyl groups;

(9) alkyl;

(10) -$(CH_2)_k$phenyl wherein k is 1 to 6;

(11) phenyl;

(12) substituted phenyl wherein the substituents are selected from the group consisting of: halo, NO_2, -OH, $-OCH_3$, $-NH_2$, $-NHR^{22}$, $-N(R^{22})_2$, alkyl, $-O(CH_2)_t$phenyl (wherein t is from 1 to 3), and $-O(CH_2)_t$substituted phenyl (wherein t is from 1 to 3);

(13) naphthyl;

(14) substituted naphthyl, wherein the substituents are as defined for substituted phenyl above;

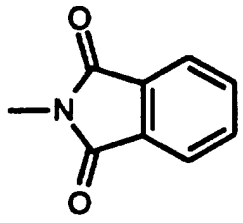
(15) bridged polycyclic hydrocarbons having from 5 to 10 carbon atoms;

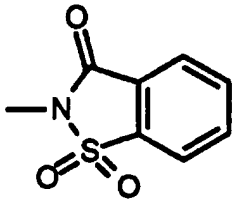
(16) cycloalkyl having from 5 to 7 carbon atoms;

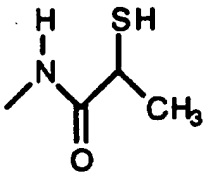
(17) heteroaryl;

(18) hydroxyalkyl;

(19) substituted pyridyl or substituted pyridyl N-oxide wherein the substituents are selected from methylpyridyl, morpholinyl, imidazolyl, 1-piperidinyl, 1-(4-methylpiperazinyl), $-S(O)_tR^{11}$, or any of the substituents given above for said substituted phenyl, and said substitutents are bound to a ring carbon by replacement of the hydrogen bound to said carbon;

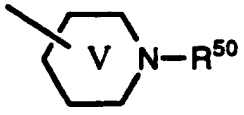
(20)  ;

(21)  ;

(22)  ;

(23) -NHC(O)-$(CH_2)_k$-phenyl or -NH(O)-$(CH_2)_k$-substitued phenyl, wherein said k is as defined above;

(24) piperidine Ring V:

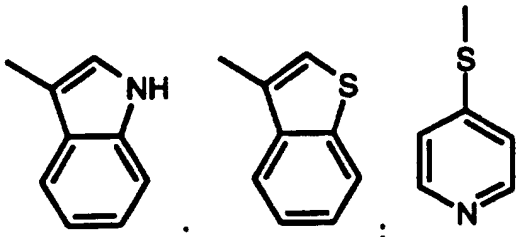


wherein R^{50} represents H, alkyl, alkylcarbonyl, alkyloxycarbonyl, haloalkyl, or -C(O)NH(R^{10}) wherein R^{10} is H or alkyl;

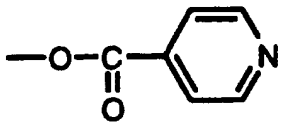
(25) -NHC(O)$CH_2C_6H_5$ or -NHC(O)CH_2-substituted-C_6H_5;

(26) -NHC(O)OC_6H_5;

(27) (28) (29)



(30) -OC(O)-heteroaryl, for example



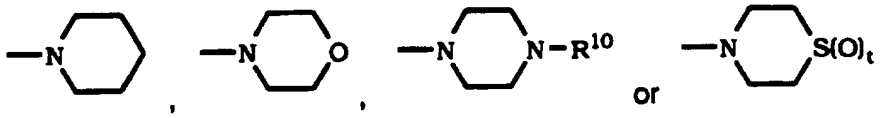
;

(31) -O-alkyl (e.g., $-OCH_3$); and

(32) $-CF_3$;

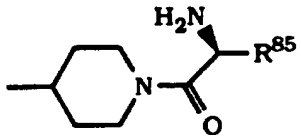
(33) -CN;

(34) a heterocycloalkyl group of the formula



; and

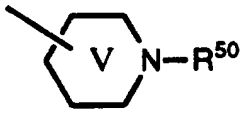
(35) a piperidinyl group of the formula



wherein R^{85} is H, alkyl, or alkyl substituted by -OH or $-SCH_3$; or

R^{20} and R^{21} taken together form a =O group and the remaining R^{46} is as defined above; or

two of R^{20}, R^{21} and R^{46} taken together form piperidine Ring V

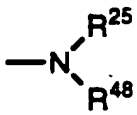


,

wherein R^{50} is as defined above;

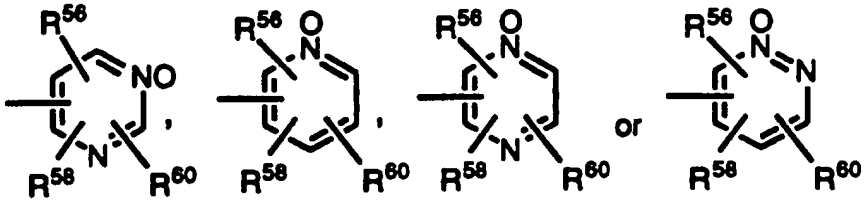
with the proviso that R^{46}, R^{20} and R^{21} are selected such that the carbon atom to which they are bound does not contain more than one heteroatom;

R^{44} represents



wherein R^{25} represents heteroaryl or aryl; and R^{48} represents H or alkyl;

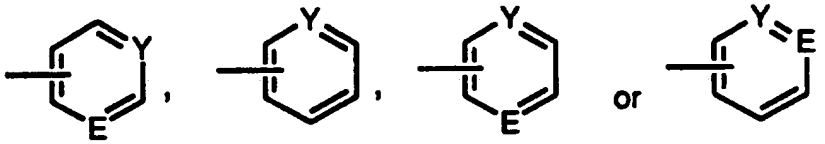
R^{54} represents an N-oxide heterocyclic group of the formula (i), (ii), (iii) or (iv):



(i) (ii) (iii) (iv)

wherein R^{56}, R^{58}, and R^{60} are the same or different and each is independently selected from H, halo, $-CF_3$, $-OR^{10}$, $-C(O)R^{10}$, $-SR^{10}$, $-S(O)_eR^{11}$ (wherein e is 1 or 2), $-N(R^{10})_2$, $-NO_2$, $-CO_2R^{10}$, $-OCO_2R^{11}$, $-OCOR^{10}$, alkyl, aryl, alkenyl or alkynyl, which alkyl may be substituted with $-OR^{10}$, $-SR^{10}$ or $-N(R^{10})_2$ and which alkenyl may be substituted with OR^{11} or SR^{11}; or

R^{54} represents an N-oxide heterocyclic group of the formula (ia), (iia), (iiia) or (iva):

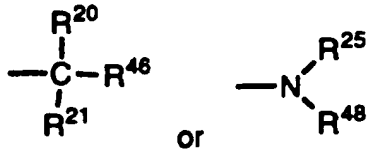


(ia) (iia) (iiia) (iva)

wherein Y represents N^+-O^- and E represents N; or

R^{54} represents an alkyl group substituted with one of said N-oxide heterocyclic groups (i), (ii), (iii), (iv), (ia), (iia), (iiia) or (iva).

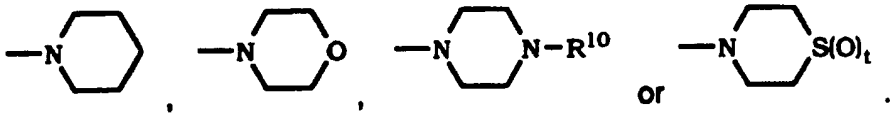
2. A compound of Claim 1wherein R^5, R^6, R^7 and R^8 are all H, and R is a group of the formula



wherein R^{20}, R^{21}, R^{25}, R^{46} and R^{48} are as defined in claim 1.

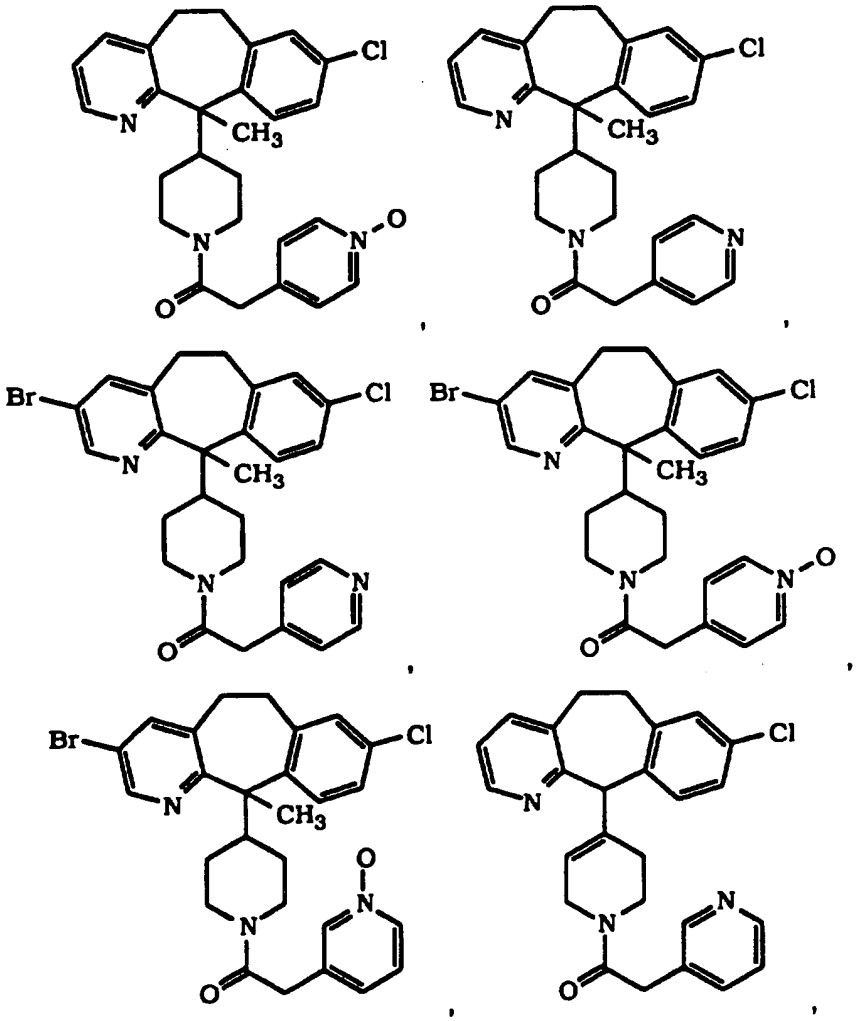
3. A compound of Claim 2 wherein: R^1 and R^2 are independently H, alkyl, alkenyl, halo, $-NHC(O)R^{10}$ or $-NHSO_2R^{10}$; R^3 and R^4 are independently H or halo; and R is a group of the formula

wherein R^{20} and R^{21} are both H, and R^{46} is 3-pyridyl, 4-pyridyl, 3-pyridyl N-oxide, 4-pyridyl N-oxide, 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-N-methylpiperazinyl, triazolyl or a heterocycloalkyl of the formula

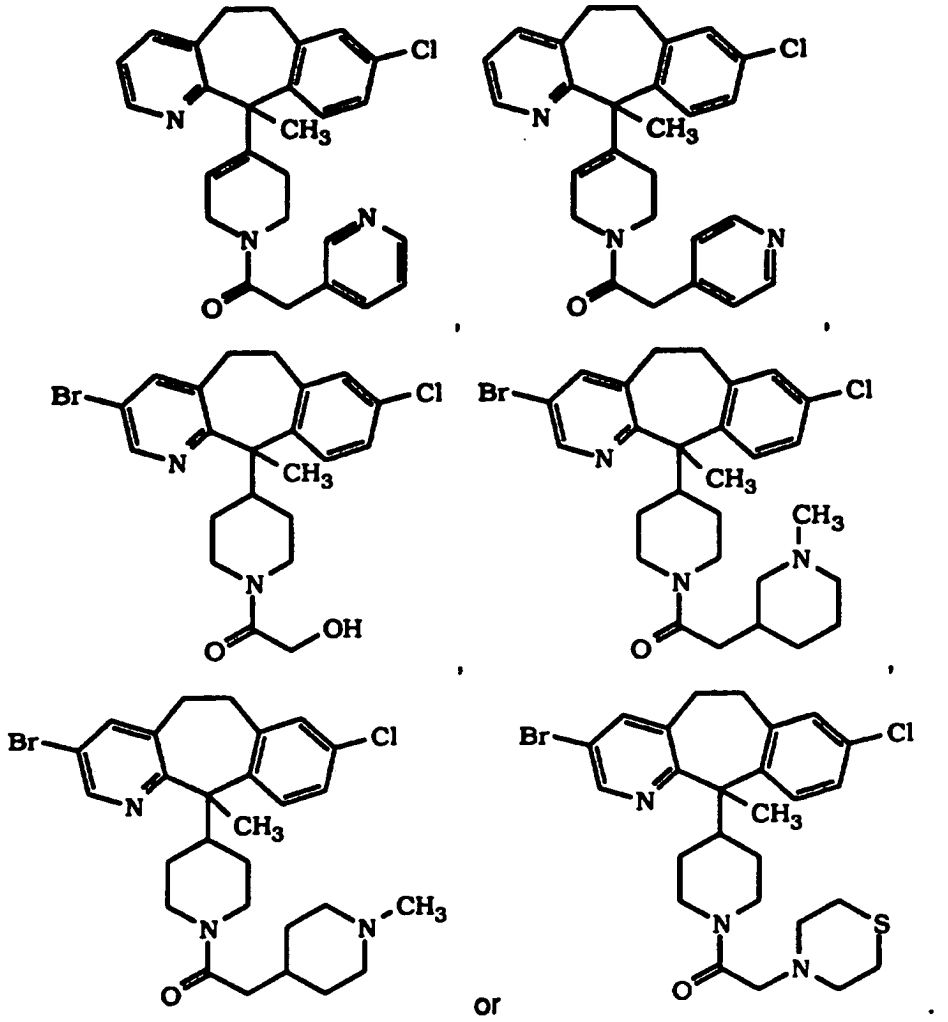


or .

4. A compound of Claim 1 selected from :



,



or

5. A method for inhibiting the abnormal growth of cells comprising administering an effective amount of a compound of Claim 1.

6. The method of Claim 5 wherein the the cells inhibited are tumor cells expressing an activated ras oncogene.

7. The method of Claim 5 wherein the cells inhibited are pancreatic tumor cells, lung cancer cells, myeloid leukemia tumor cells, thyroid follicular tumor cells, myelodysplastic tumor cells, epidermal carcinoma tumor cells, bladder carcinoma tumor cells or colon tumors cells.

8. The method of Claim 5 wherein the inhibition of the abnormal growth of cells occurs by the inhibition of farnesyl protein transferase.

9. The method of Claim 5 wherein the inhibition is of tumor cells wherein the Ras protein is activated as a result of oncogenic mutation in genes other than the Ras gene.

10. A pharmaceutical composition for inhibiting the abnormal growth of cells comprising an effective amount of compound of Claim 1 in combination with a pharmaceutically acceptable carrier.

11. The use of a compound of Claim 1 for the manufacture of a medicament for use in inhibiting the abnormal growth of cells.

12. The use of a compound of Claim 1 for inhibiting the abnormal growth of cells.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/03313

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/04 A61K31/445 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 11034 (WELLCOME FOUND) 9 July 1992 cited in the application see claims	1-3,5-12
A	US,A,4 282 233 (VILANI FRANK J) 4 August 1981 see the whole document	1,5-12
A	EP,A,0 270 818 (SCHERING CORP) 15 June 1988 see claims	1-3,5-12
P,X	WO,A,95 15949 (SCHERING CORP) 15 June 1995 see claims	1-12
P,X	WO,A,95 10516 (SCHERING CORP) 20 April 1995 see claims	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 1996	18. 07. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir ational application No.
PCT/US96/03313

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 5-9 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Inte nal Application No
PCT/US 96/03313

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9211034	09-07-92	AU-B-	665341	04-01-96
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		CA-A-	2098198	18-06-92
		EP-A-	0563134	06-10-93
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		DE-T-	3750929	01-06-95
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		OA-A-	9546	31-01-93
		WO-A-	8803138	05-05-88
		US-A-	5089496	18-02-92
		US-A-	5438062	01-08-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte nal Application No
PCT/US 96/03313

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0270818		ZA-A-	8708128	29-04-88
WO-A-9515949	15-06-95	US-A-	5464840	07-11-95
WO-A-9510516	20-04-95	AU-B-	7970394	04-05-95